Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
February 13, 2013

Table of Contents

Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document

P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Benzodiazepines and barbiturates with the exception of those specified by the Alabama Medicaid Agency
- Agents used to promote smoking cessation, unless authorized for pregnant females or plan first recipients
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are in Non-preferred status or if they required PA prior to the PDL

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

- **Appropriate Diagnosis:** Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-9 code(s) may be used. Use of ICD-9 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic, OTC or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic, OTC or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic, OTC or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, OTC, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Antilipemic Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred lipid lowering agents, either generic, OTC or brand, within the past 6 months, or have a documented allergy or contraindication to all preferred agents in this class.

- For Zetia®, if prior usage requirements have not been met, approval may be obtained for adjunctive therapy to a current lipid lowering drug.

Stable Therapy

- Approval may be given for children age 18 years and under who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 6 months for initial request and up to 12 months for renewal requests.

Electronic Prior Authorization (PA)

- Antilipemic agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Cardiac Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed 30-day treatment trials with at least two prescribed and preferred cardiac agents in this class, either generic, OTC or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

- To meet these prior usage requirements, drugs within this specific classification must be judged against others in the same class (AHFS specific).

  - For example, to qualify for a non-preferred cardiotonic, the patient must have met prior usage requirements of 30-day treatment trials with two other preferred cardiotonic agents, either generic, OTC or brand.

  - For Ranexa®, in lieu of prior usage requirements, approval may be obtained for adjunctive therapy to a current antianginal drug.

Stable Therapy

- Approval may be given for those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Cardiac agents are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

Platelet-Aggregation Inhibitors

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

The patient must also have failed 30-day treatment trials with at least 2 prescribed and preferred platelet-aggregation inhibitors in this class, either generic, OTC, or brand, within the past 6 months or have a documented allergy or contraindication to all preferred agents in this class.

Stable Therapy

- Approval may be given to those who have documented stable therapy on the requested medication for 60 consecutive days or greater.

Medical Justification

- Acceptable medical justification consists of specific clinical diagnoses for 1st line treatment by certain branded products in lieu of prior usage, allergy, contraindication or intolerance to the use of aspirin, cilostazol, ticlopidine and dipyridamole.

- Clinical literature and guidelines support the use of Aggrenox®, Effient® and Plavix® for specific 1st line indications; these indications include acute coronary syndrome, acute myocardial infarction (NSTEMI and STEMI), peripheral arterial occlusive disease (PAD, PVD), transient ischemia or ischemic stroke due to thrombosis/embolism, and percutaneous coronary interventions (balloon angioplasty, laser angioplasty, intra-coronary stents, other catheter devices treating coronary atherosclerosis).

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (PA)

- Platelet-aggregation inhibitors are included in the electronic PA program.

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

February 13, 2013
9:00 a.m. – 2:00 p.m.

1. Opening remarks…………………………………………………………………………….Chair
2. Approval of November 14, 2012 P&T Committee Meeting minutes…………………………….Chair
3. Pharmacy program update...…......................Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives (prior to each respective class review)
5. Pharmacotherapy class re-reviews from Novmember 2012 meeting…......University of Massachusetts Clinical Pharmacy Services
    - First Generation Antihistamines
        - Ethanolamine Derivatives-AHFS 040404
        - Ethylenediamine Derivatives-AHFS 040408
        - Propylamine Derivatives-AHFS 040420
    - Estrogens-AHFS 681604
    - Alpha Glucosidase Inhibitors-AHFS 682002
    - Amylinomimetics-AHFS 682003
    - Biguanides-AHFS 682004
    - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors-AHFS 682005
    - Incretin Mimetics-AHFS 682006
    - Insulins-AHFS 682008
    - Meglitinide-AHFS 682016
    - Sulfonylureas-AHFS 682020
    - Thiazolidinediones-AHFS 682028
    - Antidiabetic Agents, Miscellaneous-AHFS 682092
    - Multivitamin Preparations: Prenatal Vitamins-AHFS 882800
6. Pharmacotherapy class re-reviews……………………………….………University of Massachusetts Clinical Pharmacy Services
    - Platelet-aggregation Inhibitors – AHFS 201218
    - Antiarrhythmic Agents – AHFS 240404
    - Cardiotonic Agents – AHFS 240408
    - Cardiac Drugs, Miscellaneous – AHFS 240492
    - Bile Acid Sequestrants – AHFS 240604
    - Cholesterol Absorption Inhibitors – AHFS 240605
    - Fibric Acid Derivatives – AHFS 240606
    - HMG-CoA Reductase Inhibitors – AHFS 240608
    - Antilipemic Agents, Miscellaneous – AHFS 240692
    - Nitrites and Nitrates – AHFS 241208
7. Results of voting announced…………..………...............……………………….……………….Chair
8. Next meeting date
    - May 15, 2013
9. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Platelet-Aggregation Inhibitors
AHFS Class 201218
February 13, 2013

I. Overview

The platelet-aggregation inhibitors play a major role in the management of cardiovascular, cerebrovascular and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes, angina, intermittent claudication, myocardial infarction, stroke and transient ischemic attack. In addition, they are indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery.[1-9]

The platelet-aggregation inhibitors exert their pharmacologic effects through several different mechanisms. Aspirin, a salicylate, causes irreversible inhibition of platelet cyclooxygenase, which prevents the formation of thromboxane A_2, a platelet aggregant and potent vasoconstrictor.[10] Clopidogrel and ticlopidine are both thienopyridines, which work by blocking the adenosine diphosphate receptors found on platelets, leading to a subsequent inhibition of both platelet aggregation and activation.[6,8] The platelet inhibition effects of thienopyridines are delayed; therefore, a loading dose is typically required with these agents.[10] Prasugrel is a third generation thienopyridine adenosine diphosphate receptor antagonist; therefore, it has a similar mechanism of action to that of clopidogrel and ticlopidine. Prasugrel has been reported to be the most potent of these agents with a 10 mg dose of prasugrel being approximately 2.5 to 2.7 times more potent than a 75 mg dose of clopidogrel in inhibiting platelet aggregation and thrombus formation.[11] This reported greater efficacy in platelet inhibition is due to the difference in cytochrome activation between the agents. Clopidogrel requires a multi-step cytochrome activation process, whereas prasugrel requires only a single step.[12] Prasugrel has been shown to have more desirable characteristics when compared to clopidogrel with regards to drug-drug interactions and interpatient enzyme variability. Looking more specifically at drug-drug interactions, potent cytochrome P450 (CYP) 3A4 inhibitors have been shown to affect clopidogrel; however, no effect has been seen with prasugrel, suggesting that no dosage adjustments are necessary when faced with this type of interaction. Regarding polymorphism, studies have shown that clinical outcomes with prasugrel are not affected by patient genetic variations of the CYP2C9 and 2C19 isoenzymes, which have been reported with clopidogrel.[13] The newest platelet inhibitor to be approved by the Food and Drug Administration, ticagrelor, also works in a similar manner to the other thienopyridine platelet inhibitors. Specifically, ticagrelor is a cyclopentyltriazolopyrimidine, and the agent and its equipotent active metabolite reversibly bind to the $P2Y_{12}$ receptor located on the surface of platelets, preventing platelet signal transduction and activation.[2,5] In contrast to ticagrelor, the other available thienopyridines work via the irreversible binding to the $P2Y_{12}$ receptor. In addition, these agents are all prodrugs, while ticagrelor is not. Therefore, ticagrelor does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other platelet inhibitors.[5,6,8] When compared to clopidogrel, ticagrelor resulted in lower platelet receptor expression and a greater extent of inhibition of platelet aggregation, suggesting increased potency at the $P2Y_{12}$ receptor.[14]

The mechanism of action of dipyridamole is not completely understood; however, it may involve its ability to increase the concentrations of adenosine, a platelet aggregation inhibitor and a coronary vasodilator, and cyclic adenosine monophosphate, which decreases platelet activation.[2,9] Cilostazol inhibits phosphodiesterase activity and suppresses the degradation of cyclic-3',5'-adenosine monophosphate in platelets and blood vessels.[7]

The platelet-aggregation inhibitors that are included in this review are listed in Table 1. Currently, cilostazol, clopidogrel, dipyridamole, and ticlopidine are the platelet-aggregation inhibitors that are available generically. Aspirin, which is available over-the-counter, is also available as a branded fixed-dose combination product with extended-release dipyridamole. This review encompasses all dosage forms and strengths. This class was last reviewed in August 2010.

Table 1. Platelet-Aggregation Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Aspirin	chewable tablet, delayed-release	Ecotrin®*‡, Stanback	aspirin

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
	tablet, packet, rectal suppository, tablet	Analgesic®‡	
Cilostazol	tablet	Pletal®*	cilostazol
Clopidogrel	tablet	Plavix®*	clopidogrel
Dipyridamole	injection, tablet	Persantine®*	dipyridamole
Prasugrel	tablet	Effient®	none
Ticagrelor	tablet	Brilinta®	none
Ticlopidine	tablet	N/A	ticlopidine
Combination Products			
Aspirin and dipyridamole	extended-release capsule	Aggrenox®	none

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.
PDL=Preferred Drug List
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the platelet-aggregation inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Platelet-Aggregation Inhibitors

Clinical Guideline	Recommendations
US Preventative Services Task Force: **Aspirin for the Prevention of Cardiovascular Disease: U.S. Preventive Services Task Force Recommendation Statement[15] (2009)**	• Men aged 45 to 79 years and women 55 to 79 years should use aspirin when potential benefit of reducing myocardial infarction (MI) outweighs the potential harm of increase risk in gastrointestinal hemorrhage. • There is insufficient evidence to assess the risk to benefit ratio of aspirin in patients 80 years of age and older • Aspirin is not recommended as part of cardiovascular disease prevention in women younger than 55 years and men younger than 45 years.
American College of Chest Physicians: **Antithrombotic Therapy and Prevention of Thrombosis, 9th edition[10] (2012)**	Antithrombotic therapy for atrial fibrillation (AF) • Patients with AF, including those with paroxysmal AF, who are at low risk of stroke: no therapy is suggested over antithrombotic therapy. For patients who choose antithrombotic therapy, aspirin is suggested over oral anticoagulation or combination therapy with aspirin and clopidogrel. • Patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke: oral anticoagulation is recommended over no therapy. Oral anticoagulation is suggested over aspirin or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel are suggested over aspirin. • Patients with AF, including those with paroxysmal AF, who are at high risk of stroke: oral anticoagulation is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel is recommended over aspirin. • Patients with AF, including those with paroxysmal AF: for recommendations in favor of oral anticoagulation, dabigatran 150 mg twice daily is suggested over adjusted-dose vitamin K antagonist (VKA) therapy (target international normalized ratio [INR] range, 2.0

Clinical Guideline	Recommendations

	to 3.0).
	• Patients with AF and mitral stenosis: adjusted-dose VKA therapy is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take adjusted-dose VKA therapy, combination therapy with aspirin and clopidogrel is recommended over aspirin alone.
	• Patients with AF and stable coronary artery disease and who choose oral anticoagulation: adjusted-dose VKA therapy alone is suggested over the combination of adjusted-dose VKA therapy and aspirin.
	• Patients with AF at high risk of stroke during the first month after placement of a bare-metal stent or the first three to six months after placement of a drug-eluting stent: triple therapy (e.g., VKA therapy, aspirin, and clopidogrel) is suggested over dual antiplatelet therapy (e.g., aspirin and clopidogrel). After this initial period, a VKA plus a single antiplatelet agent is suggested over a VKA alone. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.
	• Patients with AF at intermediate risk of stroke during the first 12 months after placement of a stent: dual antiplatelet therapy is suggested over triple therapy. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.
	• Patients with AF at intermediate to high risk of stroke who experience an acute coronary syndrome (ACS) and do not undergo stent placement, for the first 12 months: adjusted-dose VKA therapy plus single antiplatelet therapy is suggested over dual antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.
	• Patients with AF at low risk of stroke: dual antiplatelet therapy is suggested over adjusted-dose VKA therapy plus single antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.
	• Patients with AF being managed with a rhythm control strategy: it is suggested that antithrombotic therapy decisions follow the general risk-based recommendations for patients with nonrheumatic AF, regardless of the apparent persistence of normal sinus rhythm.
	• Patients with atrial flutter: it is suggested that antithrombotic therapy decisions follow the same risk-based recommendations as for AF.
	
	<u>Antithrombotic therapy for ischemic stroke</u>
	• In patients with acute ischemic stroke or transient ischemic attack (TIA), early (within 48 hours) aspirin 160 to 325 mg is recommended over therapeutic parenteral anticoagulation.
	• In patients with a history of noncardioembolic ischemic stroke or TIA, aspirin (75 to 100 mg daily), clopidogrel (75 mg daily), aspirin/dipyridamole extended-release (ER) (25 mg/200 mg twice daily) or cilostazol (100 mg twice daily) is recommended over oral anticoagulants, the combination of clopidogrel plus aspirin or triflusal.
	    ○ Clopidogrel or aspirin/dipyridamole ER is recommended over aspirin or cilostazol.
	• In patients with a history of ischemic stroke or TIA and AF, oral anticoagulation with dabigatran 150 mg twice daily is recommended over VKA therapy.
	    ○ In patients who are unable to or choose not to take an oral anticoagulant, the combination of aspirin plus clopidogrel is

Clinical Guideline	Recommendations
	recommended over aspirin alone. <u>Primary and secondary prevention of cardiovascular disease</u> • Patients ≥50 years of age without symptomatic cardiovascular disease: low dose aspirin (75 to 100 mg/day) is suggested over no aspirin therapy. • Patients with established coronary artery disease: long term single antiplatelet therapy with aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended over no antiplatelet therapy, and single antiplatelet therapy is suggested over dual antiplatelet therapy. • Patients in the first year after ACS who have not undergone percutaneous coronary intervention (PCI): dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day or clopidogrel 75 mg/day plus low dose aspirin 75 to 100 mg/day) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients in the first year after an ACS who have undergone PCI with stent placement: dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day, clopidogrel 75 mg/day plus low dose aspirin, or prasugrel 10 mg/day plus low dose aspirin) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who do not undergo stenting: warfarin plus low dose aspirin (75 to 100 mg/day) is recommended over single antiplatelet therapy or dual antiplatelet therapy for the first three months. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, single antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus, who undergo bare-metal stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for one month is suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the second and third month post-bare-metal stent is suggested over alternative regimens and alternative time frames for warfarin use. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients with anterior MI and left ventricular thrombus, or at high risk for left ventricular thrombus who undergo drug-eluting stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for up to three to six months is suggested over alternative regimens and alternative durations of warfarin therapy. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective PCI with placement of bare-metal stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for one month is recommended over single antiplatelet therapy. For the subsequent 11 months, dual antiplatelet therapy with combination low dose aspirin 75 to 100 mg/day and

Clinical Guideline	Recommendations
	clopidogrel 75 mg/day is suggested over single antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. • Patients who have undergone elective PCI with placement of drug-eluting stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for three to six months is recommended over single antiplatelet therapy. After three to six months, continuation of dual antiplatelet therapy with low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested to be continued until 12 months over antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients who have undergone elective bare-metal stent or drug-eluting stent placement: low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is recommended over cilostazol in addition to these drugs. Aspirin 75 to 100 mg/day or clopidogrel 75 mg/day as part of dual antiplatelet therapy is suggested over the use of either drug with cilostazol. Cilostazol 100 mg twice daily as a substitute for either low dose aspirin or clopidogrel as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class is suggested. • Patients with coronary artery disease undergoing elective PCI but no stent placement: for the first month dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations. • Patients with systolic left ventricular dysfunction without established coronary artery disease and no left ventricular thrombus: it is suggested that antiplatelet therapy and warfarin not be used. • Patients with systolic left ventricular dysfunction without established coronary artery disease with identified acute left thrombus: moderate intensity warfarin for at least three months is suggested. • Patients with systolic left ventricular dysfunction and established coronary artery disease: recommendations are as per the established coronary artery disease recommendations. <u>Antithrombotic therapy in peripheral artery disease (PAD)</u> • In patients with asymptomatic PAD, aspirin 75 to 100 mg daily is recommended. • In patients with symptomatic PAD, long-term therapy with aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) is recommended for secondary prevention of cardiovascular events. Dual antiplatelet therapy or the combination of an antiplatelet agent with moderate-intensity warfarin is not recommended. • Use of cilostazol in addition to aspirin or clopidogrel is recommended in patients with intermittent claudication refractory to exercise therapy and smoking cessation. • Use of prostanoids in addition to aspirin or clopidogrel is recommended in patients with symptomatic PAD and critical leg ischemia who are not candidates for vascular intervention. • In patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, long-term therapy with aspirin or clopidogrel is recommended over dual antiplatelet therapy. • Following peripheral artery bypass graft surgery, long-term therapy

Clinical Guideline	Recommendations

	with aspirin or clopidogrel is recommended over the combination of antiplatelet agent plus warfarin. Clopidogrel plus aspirin for one year is recommended in patients undergoing below-knee bypass graft surgery with prosthetic grafts.
	• In patients with asymptomatic carotid stenosis, aspirin 75 to 100 mg daily is recommended.
	• In patients with symptomatic carotid stenosis, long-term therapy with clopidogrel (75 mg daily) or aspirin/dipyridamole ER (25 mg/200 mg twice daily) is recommended over aspirin (75 to 100 mg daily).
	
	<u>Antithrombotic and thrombolytic therapy for valvular disease</u>
	• Antithrombotic therapy in the first three months after surgery:
	  ○ In patients with aortic bioprosthetic valves, who are in sinus rhythm and have no other indication for VKA therapy, aspirin (50 to 100 mg/day) over VKA therapy is suggested in the first three months.
	  ○ In patients with transcatheter aortic bioprosthetic valves, aspirin (50 to 100 mg/day) plus clopidogrel (75 mg/day) is suggested over VKA therapy and over no antiplatelet therapy in the first three months.
	  ○ In patients with a bioprosthetic valve in the mitral position, VKA therapy over no VKA therapy for the first three months after valve insertion is suggested.
	• Long-term antithrombotic therapy for patients with bioprosthetic valves:
	  ○ In patients with bioprosthetic valves in normal sinus rhythm, aspirin therapy over no aspirin therapy after three months postoperative is suggested.
	• Early postoperative bridging to intermediate/long-term therapy (postoperative day 0 to 5):
	  ○ In patients with mechanical heart valves, bridging with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) over intravenous (IV) therapeutic UFH until stable on VKA therapy.
	• Long-term antithrombotic therapy for patients with mechanical valves:
	  ○ VKA therapy is recommended over no VKA therapy for long-term management.
	• Intensity of VKA therapy for patients with mechanical aortic valve prostheses:
	  ○ VKA therapy at a target of 2.5 over lower targets is suggested. A target of 2.5 is recommended over higher targets.
	• Intensity of VKA therapy for patients with mechanical mitral valve prostheses:
	  ○ VKA therapy with a target of 3.0 over lower INR targets is suggested.
	• Intensity of VKA therapy in patients with double mechanical valve or with additional risk factors:
	  ○ VKA therapy with a target of 3.0 is suggested over target INR 2.5.
	• Antiplatelet agent in addition to VKA therapy for patients with mechanical aortic or mitral valve prostheses:
	  ○ Patients who are at low risk of bleeding, adding over not adding an antiplatelet agent such as low-dose (50 to 100 mg/day) to VKA therapy is suggested.
	• For patients with mechanical aortic or mitral valves VKA therapy over

Clinical Guideline	Recommendations
	antiplatelet agents is recommended. • In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, the use of antiplatelet therapy for the first three months is suggested over VKA therapy. • In patients undergoing aortic valve repair, aspirin (50 to 100 mg/day) is suggested over VKA therapy.

American Heart Association/American Stroke Association:
Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[16] (2011)
	<u>Antithrombotic therapy for noncardioembolic stroke or TIA (specifically, atherosclerotic, lacunar, or cryptogenic infarcts)</u>
	• The use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events.
	• Aspirin (50 to 325 mg/day) monotherapy, the combination of aspirin 25 mg and dipyridamole ER 200 mg twice-daily and clopidogrel (75 mg/day) monotherapy are all acceptable options for initial therapy. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.
	• The risk of hemorrhage is increased when aspirin is added to clopidogrel; therefore, the combination is not recommended for routine secondary prevention after ischemic stroke or TIA.
	• For patients allergic to aspirin, clopidogrel is reasonable.
	• For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been studied in patients who have had an event while receiving aspirin.
	
	<u>Recommendations for patients with cardioembolic stroke types</u>
	• AF:
	  ○ For patients with ischemic stroke or TIA with paroxysmal or permanent AF, anticoagulation with a VKA (target INR, 2.0 to 3.0) is recommended.
	  ○ For patients unable to take oral anticoagulants, aspirin alone is recommended.
	  ○ The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin.
	  ○ For patients with AF at high risk for stroke who require temporary interruption of oral anticoagulation, bridging therapy with a LMWH agent administered subcutaneously is reasonable.
	• Acute MI and left ventricular thrombus:
	  ○ Patients with ischemic stroke or TIA in the setting of an acute MI complicated by left ventricular mural thrombus formation should be treated with oral anticoagulation (target INR, 2.5; range, 2.0 to 3.0) for at least three months.
	• Cardiomyopathy:
	  ○ In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction, the benefit of warfarin has not been established.
	  ○ Warfarin (INR, 2.0 to 3.0), aspirin (81 mg/day), clopidogrel (75 mg/day), or the combination of aspirin (25 mg twice-daily) plus ER dipyridamole (200 mg twice-daily) may be considered to prevent recurrent ischemic events in patients

Clinical Guideline	Recommendations

	with pervious ischemic stroke or TIA and cardiomyopathy.
	• Native valvular heart disease:
	  ○ For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable with an INR target range of 2.5 (range, 2.0 to 3.0).
	  ○ To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin.
	  ○ For patients with ischemic stroke or TIA and native aortic or non-rheumatic mitral valve disease who do not have AF, antiplatelet therapy may be reasonable.
	  ○ For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered.
	  ○ For patients with mitral valve prolapse who have ischemic stroke or TIA, long-term antiplatelet therapy may be considered.
	• Prosthetic heart valves:
	  ○ For patients with ischemic stroke or TIA who have mechanical prosthetic heart valves, warfarin is recommended with a target INR of 3.0 (range, 2.5 to 3.5).
	  ○ For patients with prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 to 100 mg/day in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range, 2.5 to 3.5) is reasonable if the patient is not at high risk of bleeding.
	  ○ For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR 2.0 to 3.0) may be considered.

American College of Cardiology Foundation/American Heart Association:
2012 American College of Cardiology Foundation/American Heart Association Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update)[17] (2012)
	Early hospital care-antiplatelet therapy
	• Aspirin should be administered as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it.
	• A loading dose followed by daily maintenance dose of clopidogrel, prasugrel or ticagrelor should be administered to patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.
	• Patients with a definite diagnosis who are at medium or high risk and in whom an initial invasive strategy is selected should receive dual antiplatelet therapy on presentation. Aspirin should be initiated on presentation, and the choice of a second antiplatelet agent to be added to aspirin on presentation should include one of the following:
	  ○ Before PCI: clopidogrel, ticagrelor or an IV glycoprotein (GP) IIb/IIIa inhibitor.
	  ○ At the time of PCI: clopidogrel, prasugrel, ticagrelor or an IV GP IIb/IIIa inhibitor.
	• For an initial conservative strategy, clopidogrel or ticagrelor (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for up to one year.
	• If recurrent symptoms/ischemia, heart failure or serious arrhythmias subsequently appear after an initial conservative strategy, diagnostic angiography should be performed. An IV GP IIb/IIIa inhibitor, clopidogrel or ticagrelor should be added to aspirin and anticoagulant therapy before diagnostic angiography.
	• A loading dose of $P2Y_{12}$ receptor inhibitor is recommended for whom

Clinical Guideline	Recommendations
	PCI is planned. Regimens include one of the following: ○ Clopidogrel 600 mg given as early as possible before or at the time of PCI. ○ Prasugrel 60 mg given promptly and no later than one hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI. ○ Ticagrelor 180 mg given as early as possible before or at the time of PCI. • The duration of maintenance dose of $P2Y_{12}$ receptor inhibitor therapy should be as follows: ○ Patients undergoing PCI: clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily for at least 12 months. ○ If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered. • If recurrent ischemia discomfort with a $P2Y_{12}$ receptor inhibitor, aspirin and anticoagulant therapy is experienced with an initial conservative strategy, it is reasonable to add a GP IIb/IIIa inhibitor before diagnostic angiography. • For an initial invasive strategy, it is reasonable to omit administration of an IV GP IIb/IIIa inhibitor if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least six hours earlier than planned catheterization or PCI. • For an initial conservative strategy, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy. • Prasugrel 60 mg may be considered for administration promptly upon presentation if PCI is planned, before definition of coronary anatomy if both the risk of bleeding is low and the need for coronary artery bypass graft (CABG) is considered unlikely. • The use of upstream GP IIb/IIIa inhibitors may be considered in high-risk patients already receiving aspirin and a $P2Y_{12}$ receptor inhibitor who are selected for an invasive strategy and who are not otherwise at high-risk for bleeding. • In patients with a definite diagnosis undergoing PCI as part of an early invasive strategy, the use of a loading dose of clopidogrel 600 mg, followed by a higher maintenance dose of 150 mg/day for six days, then 75 mg/day may be reasonable in patients not considered at high risk for bleeding. • Abciximab should not be administered to patients in whom PCI is not planned. • In patients at low risk for ischemic events or at high-risk of bleeding and who are already receiving aspirin and a $P2Y_{12}$ receptor inhibitor, upstream GP IIb/IIIa inhibitors are not recommended. • In patients with a history of stroke and/or TIA for whom PCI is planned, prasugrel is potentially harmful as part of dual antiplatelet therapy. <u>Additional antiplatelet and anticoagulation therapy</u> • In an initial conservative strategy with no subsequent features that would necessitate diagnostic angiography, a stress test should be performed. ○ If the patient is classified as not at low-risk, diagnostic angiography should be performed. ○ If the patient is classified as being at low-risk, the following should take place in preparation for discharge: ▪ Continue aspirin indefinitely.

Clinical Guideline	Recommendations
	▪ Continue clopidogrel or ticagrelor for up to one year. ▪ Discontinue IV GP IIb/IIIa inhibitor if started previously. ▪ Continue UFH for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to eight days, and then discontinue anticoagulant therapy. • If CABG was selected as a post-angiography management strategy, the following instructions should be followed: o Continue aspirin. o Discontinue IV GP IIb/IIIa inhibitor four hours before CABG. o Anticoagulant therapy should be managed as follows: ▪ Continue UFH. ▪ Discontinue enoxaparin 12 to 24 hours, fondaparinux 24 hours and bivalirudin three hours before CABG and dose with UFH per institutional practice. • In patients taking a $P2Y_{12}$ receptor inhibitor in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. The period of withdrawal should be at least five days in patients receiving clopidogrel or ticagrelor and at least seven days in those receiving prasugrel unless the need for revascularization and/or the net benefit of the $P2Y_{12}$ receptor inhibitor outweighs the potential risk of excess bleeding. • When PCI has been selected as a post-angiography management strategy, the following instructions should be followed: o Continue aspirin. o Administer a loading dose of a $P2Y_{12}$ receptor inhibitor if not started before diagnostic angiography. o Discontinue anticoagulant therapy after PCI for uncomplicated cases. • When medical therapy is selected as a management strategy and no significant obstructive coronary artery disease on angiography is present, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician. For patients in whom evidence of coronary atherosclerosis is present, albeit without flow-limiting stenosis, long-term treatment with aspirin and other secondary prevention measures should be prescribed. • When medical therapy is selected and coronary artery disease is present on angiography, the following approach is recommended: o Continue aspirin. o Administer a loading dose of clopidogrel or ticagrelor if not given before diagnostic angiography. o Discontinue IV GP IIb/IIIa inhibitor if started previously. o Anticoagulant therapy should be managed as follows: ▪ Continue IV UFH for at least 48 hours or until discharge if given before diagnostic angiography. ▪ Continue enoxaparin and fondaparinux for duration of hospitalization, up to eight days, if given before diagnostic angiography. ▪ Either discontinue bivalirudin or continue at a dose of 0.25 mg/kg per hour for up to 72 hours at the physician's discretion if given before diagnostic angiography. • When a conservative strategy is selected and no angiography or stress testing is performed, the following instructions should be followed:

Clinical Guideline	Recommendations
	- Continue aspirin indefinitely. - Continue clopidogrel or ticagrelor for up to 12 months. - Discontinue IV GP IIb/IIIa inhibitor if started previously. - Continue UFH for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to eight days, and then discontinue anticoagulant therapy. • When an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography, left ventricular ejection fraction should be measured. • When PCI is selected as a post-angiography management strategy, it is reasonable to administer an IV GP IIb/IIIa inhibitor if not started before diagnostic angiography, particularly for troponin-positive and/or other high-risk patients. • When PCI is selected as a management strategy, it is reasonable to omit administration of an IV GP IIb/IIIa inhibitor if bivalirudin was selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least six hours earlier. • If left ventricular ejection fraction is ≤0.4, it is reasonable to perform diagnostic angiography. • If left ventricular ejection fraction is >0.4, it is reasonable to perform a stress test. • Platelet function testing to determine platelet inhibitory response in patients on $P2Y_{12}$ receptor inhibitor therapy may be considered if results of testing may alter management. • Genotyping for a cytochrome P450 2C19 loss of function variant on $P2Y_{12}$ receptor inhibitor therapy might be considered if results of testing may alter management. • IV fibrinolytic therapy is not indicated in patients without acute ST-elevation, a true posterior MI, or a presumed new left bundle-branch block. <u>Long-term medical therapy and secondary prevention</u> • For patients treated medically without stenting, aspirin should be administered indefinitely. Clopidogrel (75 mg/day) or ticagrelor (90 mg twice daily) should be administered for up to 12 months. • For patients treated with a stent, aspirin should be continued indefinitely. The duration and maintenance dose of $P2Y_{12}$ receptor inhibitor should be: - Clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily for at least 12 months for drug eluting stent and up to 12 months for bare metal stent. - If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered. • Clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily should be given to patients recovering from unstable angina/non-ST-elevation MI (NSTEMI) when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance. • After PCI, it is reasonable to use aspirin 81 mg/day in preference to higher maintenance dose. • For patients who have an indication for anticoagulation, the addition of warfarin may be reasonable to maintain an INR of 2.0 to 3.0. • Continuation of a $P2Y_{12}$ receptor inhibitor beyond 12 months may be considered in patients following drug eluting stent placement. • Dipyridamole is not recommended as an antiplatelet in post-unstable

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>angina/NSTEMI patients because it has not been shown to be effective.</td></tr>
<tr><td>European Society of Cardiology: Guideline for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation[18] (2011)</td><td><u>Recommendations for oral antiplatelet agents</u>
• Aspirin should be given to all patients without contraindications at an initial loading dose of 150 to 300 mg; maintenance doses should be between 75 to 100 mg daily regardless of treatment strategy.
• A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications.
• A proton pump inhibitor (preferably not omeprazole) is recommended in combination with dual antiplatelet therapy in patients with a history of gastrointestinal hemorrhage or peptic ulcer, and is appropriate for patients with multiple other risk factors (e.g., Helicobacter pylori infection, age ≥65 years, concurrent use of anticoagulants or steroids).
• Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically warranted.
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate to high risk of ischemic events (e.g., elevated troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel. Clopidogrel should be discontinued when ticagrelor is initiated.
• Prasugrel (60 mg loading dose, 10 mg daily) is recommended for $P2Y_{12}$ inhibitor naïve patients (particularly diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.
• Clopidogrel (300 mg loading dose, 75 mg daily) is recommended for those who cannot receive ticagrelor or prasugrel.
    ○ A 600 mg loading dose (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for invasive strategy when ticagrelor or prasugrel is not an option.
    ○ A higher maintenance dose of 150 mg/day should be considered for the first seven days in patients managed with PCI and without increased risk of bleeding.
    ○ Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.
    ○ Genotyping and/or platelet function testing can be considered in selected cases when clopidogrel is used.
• In patients pretreated with $P2Y_{12}$ inhibitors who need to undergo nonemergency major surgery (including CABG), postponing surgery for at least five days after cessation of ticagrelor or clopidogrel, and seven days for prasugrel, if clinically feasible and unless the patient is at high risk of ischemic events should be considered.
• Ticagrelor or clopidogrel should be considered to be re-started after CABG surgery as soon as it is safe.
• The combination of aspirin with a non-steroidal anti-inflammatory is not recommended.</td></tr>
<tr><td>American College of Chest Physicians: Antithrombotic Therapy for Non-ST-Segment Elevation Acute Coronary Syndromes[19] (2008)</td><td>• For all patients presenting with non-ST-elevated acute coronary syndrome (NSTE ACS), immediate aspirin (162 to 325 mg) and then daily oral aspirin (75 to 100 mg) is recommended.
• For all NSTE ACS patients with an aspirin allergy, immediate treatment with clopidogrel, 300 mg bolus, followed by 75 mg/d is recommended indefinitely.
• For NSTE ACS patients who are at moderate or greater risk for an ischemic event and who will undergo an early invasive management</td></tr>
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<tr><td></td><td>strategy, treatment with either clopidogrel (300 mg bolus, followed by 75 mg/d) or a GP IIb/IIIa inhibitor (eptifibatide or tirofiban) is recommended.
For NSTE ACS patients who are at moderate or greater risk for an ischemic event and for whom an early conservative or a delayed invasive strategy of management is to be used, treatment with clopidogrel (300 mg bolus, followed by 75 mg/d) is recommended.
For NSTE ACS patients who undergo PCI, treatment with both clopidogrel and a GP IIb/IIIa inhibitor is recommended.
A loading dose of 600 mg of clopidogrel should be given at least 2 hours prior to the PCI, followed by 75 mg/d.
If ticlopidine is given, a loading dose of 500 mg should be given at least 6 hours prior to the planned PCI.
For PCI patients who cannot tolerate aspirin, a loading dose of clopidogrel (600 mg) or ticlopidine (500 mg) should be given at least 24 hours prior to the planned PCI.
The use of a GP IIb/IIIa antagonist is recommended for all NSTE ACS patients with at least moderate risk features undergoing PCI in whom a GP IIb/IIIa inhibitor has not been started upstream.
For NSTE ACS patients who have received clopidogrel and are scheduled for CABG, we suggest discontinuing clopidogrel for at least 5 days prior to the scheduled surgery (Grade 2A).</td></tr>
<tr><td>American College of Cardiology/American Heart Association and American College of Cardiology/American Heart Association/ Society for Cardiovascular Angiography and Interventions:
2009 Focused Update of the 2007 Focused Update and the 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction AND Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update)[20] (2009)</td><td><u>ST-segment elevation myocardial infarction (STEMI) and PCI focused update section</u>
Recommendations for the use of thienopyridines:
A loading dose of thienopyridines is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following:
At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or non-primary PCI.
Prasugrel 60 mg should be given as soon as possible for primary PCI.
For STEMI patients undergoing non-primary PCI, the following regimens are recommended:
If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice.
If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice.
If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than one hour after the PCI.
The duration of thienopyridine therapy should be as follows:
In patients receiving a stent (bare metal stent or drug eluting stent) during PCI for ACS, clopidogrel 75 mg/day or prasugrel 10 mg/day should be given for at least 12 months.</td></tr>
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Clinical Guideline	Recommendations
	▪ If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered. o In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. The period of withdrawal should be at least five days in patients receiving clopidogrel and at least seven days in patients receiving prasugrel, unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding. o Continuation of clopidogrel and prasugrel beyond 15 months may be considered in patients undergoing drug-eluting stent placement. o In STEMI patients with a prior history of stroke and TIA for whom primary PCI is planned, prasugrel is not recommended as part of a dual antiplatelet therapy regimen. Recommendations for the timing of angiography and antiplatelet therapy in unstable angina/NSTEMI • Patients with definite or likely unstable angina/NSTEMI selected for an invasive approach should receive dual-antiplatelet therapy. Aspirin should be initiated on presentation. Clopidogrel (before or at the time of PCI) or prasugrel (at the time of PCI) is recommended as a second antiplatelet agent. • It is reasonable for initially stabilized high risk patients with unstable angina/NSTEMI to undergo an early invasive strategy within 12 to 24 hours of admission. For patients not at high risk, an early invasive approach is also reasonable.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with Persistent ST-segment Elevation[21]** **(2012)**	Periprocedural antithrombotic medication in primary PCI • Aspirin oral or intravenous is recommended. • An adenosine diphosphate-receptor blocker is recommended in addition to aspirin. Options include: o Prasugrel (in clopidogrel-naïve patients, if no history of prior stroke/transient ischemic stroke, age <75 years) o Ticagrelor o Clopidogrel (preferably when prasugrel or ticagrelor are either not available or contraindicated) Routine therapies in the acute, subacute, and long-term phase of STEMI • Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. • Patients who are intolerant to aspirin, clopidogrel is indicated as an alternative to aspirin. • Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI. • Dual antiplatelet therapy with aspirin and an oral adenosine diphosphate receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of one month for patients receiving bare metal stent and six months for patients receiving drug eluting stent.
American College of Chest Physicians: **Acute ST-Segment Elevation**	• For patients with acute STEMI whether or not they receive fibrinolytic therapy, aspirin (160 to 325 mg) is recommended over no aspirin at the initial evaluation, followed by indefinite therapy (75 mg to 162 mg/d).

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<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td>Myocardial Infarction[22] (2008)</td><td>For patients with acute STEMI, clopidogrel in addition to aspirin is recommended. The recommended dose of clopidogrel is 300 mg for patients <75 years of age and 75 mg for patients >75 years of age if they receive fibrinolytic agents or no reperfusion therapy, followed by 75 mg/d for up to 28 days.
For patients with acute STEMI who have not received a coronary stent, clopidogrel 75 mg/d could be continued beyond 28 days and up to 1 year.
For patients undergoing primary PCI, clopidogrel in addition to aspirin is suggested at a dose of at least 300 mg, followed by 75 mg daily.</td></tr>
<tr><td>American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions:
2011 Guideline for Percutaneous Coronary Intervention[23] (2011)</td><td><u>Interventional pharmacotherapy-oral antiplatelet therapy</u>
Patients already taking daily aspirin therapy should take 81 to 325 mg before PCI.
Patients not on aspirin therapy should be given non-enteric aspirin 325 mg before PCI.
After PCI, use of aspirin should be continued indefinitely.
A loading dose of one of the following $P2Y_{12}$ receptor inhibitors should be given to patients undergoing PCI with stenting: clopidogrel 600 mg (ACS and non-ACS patients), prasugrel 60 mg (ACS patients), or ticagrelor 180 mg (ACS) patients.
The loading dose of clopidogrel for patients undergoing PCI after fibrinolytic therapy should be 300 mg within 24 hours and 600 mg more than 24 hours after receiving fibrinolytic therapy.
Patients should be counseled on the need for and risks of dual antiplatelet therapy before placement of intracoronary stents, especially drug-eluting stents, and alternative therapies should be pursued if patients are unwilling or unable to comply with the recommended duration of dual antiplatelet therapy.
The duration of $P2Y_{12}$ inhibitor therapy after stent implantation should generally be as follows:
In patients receiving a stent (bare metal or drug eluting stent) during PCI for ACS, $P2Y_{12}$ inhibitor therapy with one of the following options should be given for at least 12 months: clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 90 mg twice-daily.
In patients receiving drug-eluting stent for a non-ACS indication, clopidogrel 75 mg/day should be given for at least 12 months if patients are not at high risk of bleeding.
In patients receiving bare-metal stents for a non-ACS indication, clopidogrel should be given for a minimum of one month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of two weeks).
After PCI, it is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses.
If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable.
Continuation of dual antiplatelet therapy beyond 12 months may be considered in patients undergoing drug-eluting stent implantation.
Prasugrel should not be administered to patients with a prior history of stroke or TIA.
<u>Post-procedural recommendations for patients undergoing PCI</u></td></tr>
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Clinical Guideline	Recommendations
	Aspirin: • Use of aspirin should be continued indefinitely. • It is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses. $P2Y_{12}$ inhibitors: • In patients receiving a stent (bare-metal or drug-eluting stent) during PCI for ACS, therapy with either clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 90 mg twice-daily should be given for at least 12 months. • In patients receiving drug-eluting stent for a non-ACS indication, clopidogrel 75 mg/day should be given for at least 12 months if patients are not at high risk of bleeding. • In patients receiving bare-metal stent for a non-ACS indication, clopidogrel should be given for a minimum of one month and ideally up to 12 months (unless the patient is at an increased risk of bleeding; then it should be given for a minimum of two weeks). • Patients should be counseled on the importance of compliance with dual antiplatelet therapy and that therapy should not be discontinued before discussion with their cardiologist. • Proton pump inhibitors should be used in patients with a history of prior gastrointestinal bleeding who require dual antiplatelet therapy. • If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, either discontinuation (e.g., <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable. • Use of proton pump inhibitors is reasonable in patients with an increased risk of gastrointestinal bleeding (e.g., advanced age, concomitant use of warfarin, steroids, nonsteroidal anti-inflammatory drugs, *Helicobacter pylori* infection) who require dual antiplatelet therapy. • Continuation of clopidogrel, prasugrel, or ticagrelor beyond 12 months may be considered in patients undergoing placement of drug-eluting stent. • Routine use of a proton pump inhibitor is not recommended for patients at low risk of gastrointestinal bleeding, who have much less potential to benefit from prophylactic therapy. Clopidogrel genetic testing • Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel. • When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternative $P2Y_{12}$ inhibitor (e.g., prasugrel, ticagrelor) might be considered. • The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.
National Institute for Health and Clinical Excellence: **Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction[24] (2007)**	• Aspirin is recommended in all patients after a MI and should be continued indefinitely. Clopidogrel should not be offered as first-line monotherapy after a MI. • Clopidogrel combined with low dose aspirin for 12 months is recommended in patients who have had a NSTE ACS who are at moderate to high risk of MI or death. Thereafter, patients may be treated with low dose aspirin without clopidogrel in the absence of indication for dual antiplatelet therapy.

Clinical Guideline	Recommendations
	• Patients who have been treated with aspirin and clopidogrel within the first 24 hours of an STEMI should continue on dual antiplatelet therapy for at least four weeks. Thereafter, low-dose aspirin should be continued, and clopidogrel discontinued in the absence of indication for dual antiplatelet therapy. • If both clopidogrel and aspirin were not given during the acute phase of a MI, this combination should not routinely be initiated. • Dual antiplatelet therapy with aspirin and clopidogrel should not be used for longer than 12 months after an acute MI unless another indication for dual antiplatelet therapy exists. After a STEMI, the combination of aspirin and clopidogrel is usually recommended for a shorter duration than 12 months. • Clopidogrel monotherapy is an alternative treatment in patients with aspirin hypersensitivity. • Low dose aspirin and a proton pump inhibitor are recommended in patients with comorbid dyspepsia. A full dose proton pump inhibitor and low dose aspirin should be considered in patients with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for *Helicobacter pylori*. • Patients being treated with warfarin for another indication should continue on warfarin. Those being treated with moderate-intensity warfarin (INR 2.0 to 3.0) and are at low risk of bleeding, may be treated with aspirin. The combination of warfarin and clopidogrel is not routinely recommended.
National Institute for Health and Clinical Excellence: **Clopidogrel and Modified-Release Dipyridamole for the Prevention of Occlusive Vascular Events[25] (2010)**	• This guidance applies to people who have had an occlusive vascular event, or who have established peripheral arterial disease. This guidance does not apply to people who have had, or are at risk of, a stroke associated with AF, or who need treatment to prevent occlusive events after coronary revascularization or carotid artery procedures. • For people who have had an ischemic stroke, clopidogrel is recommended as a treatment option. For people who have a contraindication or intolerance to clopidogrel, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to both clopidogrel and aspirin, modified-release dipyridamole alone is recommended as a treatment option. • For people who have had a TIA, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to aspirin, modified-release dipyridamole alone is recommended as a treatment option. • For people who have had a MI, clopidogrel is recommended only when treatment with aspirin is contraindicated or not tolerated. • For people with peripheral arterial disease, clopidogrel is recommended as a treatment option. • For people with multi-vascular disease, clopidogrel is recommended as a treatment option. • Treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable**	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients unless contraindicated. • The use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.

Clinical Guideline	Recommendations
Angina[26] (2007)	
European Society of Cardiology: **Management of Stable Angina Pectoris[27] (2006)**	Therapy to improve prognosis • Aspirin 75 mg daily is recommended in all patients without specific contraindications (e.g., active gastrointestinal bleeding, aspirin allergy, previous aspirin intolerance). Clopidogrel is an alternative antiplatelet agent in patients who cannot take aspirin. • The use of unopposed cyclooxygenase-2 inhibition is not recommended in patients with stable angina pectoris. • Clopidogrel may be combined with aspirin after coronary stenting or an ACS for a finite period of time, but combination therapy is currently not recommended in stable angina pectoris. • Dipyridamole is not recommended for antithrombotic treatment of stable angina.

American Heart Association/American College of Cardiology Foundation: **Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2011 Update[28] (2011)**	Antiplatelet agents/anticoagulants
	• Aspirin 75 to 162 mg daily is recommended in all patients with coronary artery disease unless contraindicated.
	    • Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.
	    • Combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease.
	• A P2Y12 receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement.
	    • For patients receiving a bare-metal stent or drug-eluting stent during PCI or ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily or ticagrelor 90 mg twice daily should be given for at least 12 months.
	    • If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy after stent implantation, earlier discontinuation (e.g., 12 months) is reasonable. The risk for serious cardiovascular events because of early discontinuation of thienopyridines is greater for patients with drug-eluting stents than those with bare-metal stents.
	    • After PCI, it is reasonable to use aspirin 81 mg daily in preference to higher maintenance doses.
	• For patients undergoing CABG, aspirin should be started within six hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg daily for one year appear to be efficacious.
	    • For patients undergoing CABG, clopidogrel (75 mg daily) is a reasonable alternative in patients who are intolerant of or allergic to aspirin.
	• In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75 to 325 mg daily), clopidogrel alone (75 mg daily) or the combination of aspirin plus dipyridamole ER (25 mg and 200 mg twice daily, respectively) should be started and continued.
	• For patients with symptomatic atherosclerotic PAD of the lower extremity, antiplatelet therapy with aspirin (75 to 325 mg daily) or clopidogrel (75 mg daily) should be started and continued.
	    • The benefits of aspirin in patients with asymptomatic PAD of the lower extremities are not well established.
	• Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other VKA to treat patients with

Clinical Guideline	Recommendations
	atherosclerosis. • If there is a compelling indication for anticoagulant therapy, such as AF, prosthetic heart valve, left ventricular thrombus or concomitant venous thromboembolic disease, warfarin should be administered in addition to the low-dose aspirin (75 to 81 mg daily). • For patients requiring warfarin, therapy should be administered to achieve the recommended INR for the specific condition. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.
European Society of Cardiology, Task Force on the Use of Antiplatelet Agents in Patients With Atherosclerotic Cardiovascular Disease: **Expert Consensus Document on the Use of Antiplatelet Agents[29] (2004)**	<u>Major recommendations for individual antiplatelet agents</u> Aspirin: • Aspirin once-daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. • Because of gastrointestinal toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting. • The available evidence supports daily doses of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients (e.g., ≥3% per annum). • In clinical situations where an immediate antithrombotic effect is required (such as in ACS or in acute ischemic stroke), a loading dose of 160 to 300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of thromboxane A2-dependent platelet aggregation. • No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient. • The routine use of proton pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75 to 100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting. • Nonsteroidal anti-inflammatory drugs have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin. • Because of potential pharmacodynamic interactions between traditional nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) and aspirin, patients treated with low-dose aspirin requiring nonsteroidal ant-inflammatory drug therapy may benefit from the use of selective cyclooxegenase-2 inhibitors. Ticlopidine: • The role of ticlopidine in the present therapeutic armamentarium is uncertain. • Although there are no large head-to-head comparisons between the two thienopyridines, indirect comparisons are highly suggestive of a lower burden of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine. • In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent MI. Clopidogrel: • Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain and the drug has

Clinical Guideline	Recommendations
	not been granted a claim of "superiority" vs aspirin by regulatory authorities. • Clopidogrel 75 mg/day is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a contraindication to low-dose aspirin. • The results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial have led to Food and Drug Administration approval of a new indication for clopidogrel in patients with NSTE ACS. A loading dose of 300 mg clopidogrel should be used in this setting, followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of PCI, length of clopidogrel treatment and combination with GP IIb/IIIa antagonists. Dipyridamole: • Although the combination of low-dose aspirin and dipyridamole ER (200 mg twice-daily) is considered an acceptable option for initial therapy of patients with noncardioembolic cerebral ischemic events, there is no basis to recommend this combination in patients with ischemic heart disease.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the platelet-aggregation inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Platelet-Aggregation Inhibitors[1-9]

Indication	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Acute Coronary Syndromes								
Reduce the rate of a combined end point of cardiovascular death, myocardial infarction, or stroke, as well as the rate of a combined end point of cardiovascular death, myocardial infarction, stroke, or refractory ischemia in patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-ST-elevation myocardial infarction [NSTEMI]), including patients who are to be managed medically and those who are to be managed with coronary revascularization			✔					
Reduce the rate of death from any cause and the rate of a combined end point of death, reinfarction, or stroke in patients with ST-elevation myocardial infarction (STEMI)			✔ *					
Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome						✔		
Reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows: patients with unstable angina or NSTEMI OR patients with STEMI when managed with primary or delayed percutaneous coronary intervention					✔			
Atherothrombotic/Vascular Events								
Reduce the rate of a combined end point of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), and other vascular death in patients with a history of recent myocardial infarction, recent stroke, or established peripheral arterial disease			✔					

Indication	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation as adjunctive therapy with aspirin							✔	
Reduce postoperative thromboembolic complications of cardiac valve replacement as an adjunct to coumarin anticoagulants				✔ (tablet)				
Revascularization procedures; in patients who have undergone revascularization procedures where there is a preexisting condition for which aspirin is already indicated	✔							
Vascular indication; to reduce the risk of vascular mortality in patients with a suspected acute myocardial infarction; to reduce the combined risk of death and nonfatal myocardial infarction in patients with a previous myocardial infarction or unstable angina pectoris; to reduce the combined risk of myocardial infarction and sudden death in patients with chronic stable angina pectoris	✔							
Intermittent Claudication								
For the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance		✔						
Ischemic Stroke or Transient Ischemic Attack								
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis								✔
Reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke							✔ †	
Vascular indication; reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli	✔							
Miscellaneous Indications								
Analgesic/antipyretic; temporary relief of headache, pain, and fever caused by colds, muscle aches and pains, menstrual pain, toothache pain, and minor aches and pains of arthritis	✔							
Radionuclide myocardial perfusion study				✔ (injection)				

Indication	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Rheumatoid disease; relief of signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with systemic lupus erythematosus	✔							

*The benefit of clopidogrel for patients who undergo primary percutaneous coronary intervention is unknown.
†Because ticlopidine is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia, agranulocytosis and aplastic anemia, it should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.

IV. Pharmacokinetics

The pharmacokinetic parameters of the platelet-aggregation inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Platelet-Aggregation Inhibitors[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aspirin	50 to 75	50 to 80	Liver	Renal (6 to 36)	3 to 10
Cilostazol	87 to 100	95 to 98	Liver (% not reported)	Renal (74) Feces (20)	11 to 13
Clopidogrel	≥50	Not reported	Liver (% not reported)	Renal (50) Feces (46)	6
Dipyridamole	37 to 66	99	Liver (% not reported)	Renal (% not reported)	40 minutes (alpha), 10 hours (beta)*
Prasugrel	79	98	Liver (% not reported)	Renal (68 to 70) Feces (25 to 27)	7 to 8
Ticagrelor	36	>99	Liver (% not reported)	Renal (26) Feces (58)	7
Ticlopidine	80 to 90	98	Liver (% not reported)	Renal (60) Feces (23)	12.6

*Dipyridamole follows a two-compartment model.

V. Drug Interactions

Significant drug interactions with the platelet-aggregation inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the Platelet-Aggregation Inhibitors[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Aspirin	1	Clopidogrel	Concurrent therapy may increase the risk of life-threatening bleeding (e.g., intracranial and gastrointestinal hemorrhage) in high-risk patients with transient ischemic attack or ischemic stroke. Avoid aspirin use in high-risk patients with recent ischemic stroke or transient ischemic attack who are receiving clopidogrel.
Aspirin	1	Heparin	Aspirin can inhibit platelet aggregation and has caused bleeding. The risk of bleeding may be increased when aspirin and heparin are used together. Monitor coagulation parameters and signs of bleeding if the combination is used.
Aspirin	1	Influenza Virus Vaccine, Intranasal	Intranasal influenza virus vaccine is contraindicated in children and adolescents on aspirin therapy as the risk of Reye syndrome may be increased.
Aspirin	1	Ketorolac	Aspirin may displace ketorolac from protein binding sites and have synergistic side effects. Ketorolac is contraindicated in patients receiving

Generic Name(s)	Significance Level	Interaction	Mechanism
			aspirin due to an increased risk of serious ketorolac-related side effects.
Aspirin	1	Methotrexate	Salicylates may increase the toxic effects of methotrexate by decreasing methotrexate’s renal clearance and plasma protein binding. When salicylates are coadministered, the dose of methotrexate may need to be decreased or prolonged regimens of leucovorin rescue may be indicated. Dosage adjustment may also be guided by monitoring methotrexate plasma levels.
Aspirin	1	Nonsteroidal anti-inflammatory drugs (NSAIDs)	The pharmacologic effects of some NSAIDs may be decreased and the cardioprotective effect of low-dose uncoated aspirin may be reduced with concurrent administration of NSAIDs and aspirin. Both aspirin and NSAIDs are also gastric irritants. Consider using analgesics that do not interfere with antiplatelet effect (e.g., acetaminophen).
Aspirin	1	Rivaroxaban	Inhibition of the normal clotting mechanism may be increased. Use caution when administered concurrently, and promptly evaluate any signs or symptoms of blood loss.
Aspirin	1	Sulfonylureas	Salicylates may increase the hypoglycemic effect of sulfonylureas by several mechanisms. Salicylates reduce basal plasma glucose levels, enhance insulin secretion and inhibit acute insulin responses to glucose. Salicylates may also displace sulfonylureas from protein binding sites. Monitor the patient’s blood glucose and if hypoglycemia develops, consider decreasing the sulfonylurea dose. Consider alternative therapy with acetaminophen or an NSAID.
Aspirin	1	Warfarin	The anticoagulant activity of warfarin and the risk of hemorrhage may be enhanced by the effects of aspirin on the gastric mucosa and platelet function. If concurrent use cannot be avoided, frequently monitor the patient’s international normalized ratio and adjust the warfarin dose accordingly, especially when starting or stopping aspirin therapy.
Clopidogrel	1	Proton-pump Inhibitors	Proton pump inhibitors interfere with the metabolic conversion of clopidogrel at cytochrome P450

Generic Name(s)	Significance Level	Interaction	Mechanism
			(CYP) 2C19 to its active metabolite, thus decreasing the antiplatelet activity of clopidogrel.
Aspirin	2	Angiotensin-converting enzyme (ACE) inhibitors	Aspirin inhibits prostaglandin synthesis and may reduce the hypotensive and vasodilator effects of the ACE inhibitor. Monitor blood pressure and hemodynamic parameters if both agents are needed.
Aspirin	2	β-blockers	Salicylates may inhibit the synthesis of prostaglandins involved in the antihypertensive activity of β-blockers; therefore, the blood pressure-lowering effects of β-blockers may be reduced. In addition, the beneficial effects of β-blockers on left ventricular ejection fraction in patients with chronic heart failure may be attenuated; however, the mechanism of this interaction is not known.
Aspirin	2	Carbonic anhydrase inhibitors	Concurrent administration of carbonic anhydrase inhibitors and salicylates may result in the accumulation of carbonic anhydrase inhibitors and toxicity (e.g., central nervous system depression, metabolic acidosis). Aspirin displaces carbonic anhydrase inhibitors from plasma protein binding sites and inhibits renal clearance. Metabolic acidosis may lead to increased penetration of salicylates into the central nervous system. Minimize or avoid coadministration of salicylates and carbonic anhydrase inhibitors.
Aspirin	2	Insulin	Salicylates may potentiate the serum glucose-lowering action of insulin by increasing basal insulin concentrations and enhancing the acute insulin response to a glucose load. Blood glucose levels should be monitored and insulin regimens tailored as needed.
Aspirin	2	Probenecid	Coadministration of probenecid and aspirin may inhibit the uricosuric action of either drug alone. The mechanism of this interaction is not known but may be due to an alteration in the renal filtration of uric acid. Coadministration should be avoided to allow maximum uricosuria to be attained. Aspirin therapy dosed at non-antiinflammatory concentrations may

Generic Name(s)	Significance Level	Interaction	Mechanism
			be acceptable in patients who require both agents.
Aspirin	2	Sulfinpyrazone	Salicylates may displace sulfinpyrazone from plasma protein binding sites and may block the inhibitory effects of sulfinpyrazone on tubular reabsorption of uric acid. Patients should be counseled not to take salicylate-containing products on a regular or extended basis since the uricosuria produced by sulfinpyrazone may be suppressed.
Aspirin	2	Valproic acid	Aspirin may displace valproic acid from protein binding sites and increase the free fraction of valproic acid, leading to toxic effects. Aspirin may also alter the metabolic pathways of valproic acid. Monitor serum valproic acid concentrations (including free fraction if readily available), symptoms of valproic acid toxicity and liver enzymes when aspirin is coadministered with valproic acid.
Cilostazol	2	Clarithromycin, erythromycin	Certain macrolide antibiotics may inhibit the metabolism (CYP3A4) of cilostazol leading to increased plasma concentrations of cilostazol and resulting in increased therapeutic and adverse effects. Consider decreasing the dose of cilostazol during coadministration with certain macrolide antibiotics.
Cilostazol	2	Omeprazole	Omeprazole may inhibit the metabolism (CYP2C19) of cilostazol leading to increased plasma concentrations of cilostazol and resulting in increased therapeutic and adverse effects. Consider decreasing the dose of cilostazol during coadministration of omeprazole.
Clopidogrel	2	Ketoconazole	Ketoconazole may inhibit the isozymes (CYP3A4 and CYP3A5) that convert the prodrug clopidogrel to its active metabolite. If possible, avoid coadministration of these agents since the antiplatelet effect of clopidogrel may be inhibited.
Clopidogrel	2	Rifamycins	Clopidogrel is a progdrug that appears to be catalyzed to its active metabolite by cytochrome P450 (CYP) 3A4 and 3A5. Rifamycins are inducers of CYP3A4; therefore, they may increase the metabolic conversion of clopidogrel to its active metabolite. Carefully monitor

Generic Name(s)	Significance Level	Interaction	Mechanism
			platelet function with rifamycins are started, discontinued, or changed, and adjust the dose of clopidogrel as needed.
Clopidogrel	2	Warfarin	The mechanism by which the risk of nonfatal and fatal bleeding may be increased with combined therapy is unknown. When indicated, coadminister clopidogrel and warfarin with caution. Closely monitor coagulation and the patient for bleeding events.
Dipyridamole	2	Adenosine	Dipyridamole may potentiate the pharmacologic effects of adenosine by inhibiting the transport or metabolism of adenosine. Following rapid bolus administration of adenosine, profound bradycardia may occur.
Ticlopidine	2	Cyclosporine	Through an unknown mechanism, ticlopidine decreases cyclosporine whole blood concentrations and pharmacologic effects. If ticlopidine therapy is started or discontinued, consider frequent monitoring of cyclosporine blood concentrations. Adjust the dose of cyclosporine or discontinue ticlopidine as indicated.
Ticlopidine	2	Hydantoins	Ticlopidine may inhibit hydantoin metabolism thereby increasing plasma hydantoin concentrations and adverse effects. Monitor hydantoin levels and make dosage adjustments as needed. Also, observe the patient’s clinical response when starting, stopping, or changing the dose of ticlopidine.
Ticlopidine	2	Theophyllines	Ticlopidine may impair theophylline elimination. Theophylline levels may increase and lead to toxicity (e.g., nausea, vomiting, seizures and arrhythmias). Monitor theophylline serum levels when ticlopidine is added or withdrawn from a patient’s regimen and tailor dosages as needed.

Significance Level 1 = major severity.
Significance Level 2 = moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the platelet-aggregation inhibitors are listed in Table 6. The boxed warnings for the platelet-aggregation inhibitors are listed in Tables 7 through 11.

Table 6. Adverse Drug Events (%) Reported with the Platelet-Aggregation Inhibitors[1-9]

Adverse Events	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Cardiovascular								
Angina pectoris	-	-	-	✔	-	-	-	<1
Arrhythmia	-	-	-	-	-	-	-	<1
Atrial fibrillation/flutter	✔	<2	1 to 3	-	3	4.2	-	-
Bradycardia	-	-	-	-	3	-	-	-
Cardiac arrest	-	<2	-	-	-	-	-	-
Cardiac failure	-	-	1 to 3	-	-	-	-	2
Chest pain	-	-	8	-	3	3.1	-	-
Conduction defect	✔	-	-	-	-	-	-	-
Congestive heart failure	-	<2	-	-	-	-	-	-
Coronary artery spasm	✔	-	-	-	-	-	-	-
Dysrhythmias	✔	-	-	-	-	-	-	-
Edema	✔	-	4	-	3	-	-	-
Hypertension	-	-	4	-	8	3.8	-	-
Hypotension	✔	<2	-	✔	4	3.2	-	-
Myocardial infarction/ischemia	-	<2	-	-	-	-	-	-
Nodal arrhythmia	-	<2	1 to 3	-	-	-	-	-
Palpitation	-	5 to 10	-	✔	-	-	-	-
Peripheral edema	-	7 to 9	-	-	-	-	-	-
Postural hypotension	-	<2	-	-	-	-	-	-
QTc prolongation	-	<2	-	-	-	-	-	-
Supraventricular tachycardia	-	<2	-	-	-	-	-	-
Syncope	-	<2	1 to 3	-	-	-	-	1
Tachycardia	✔	4	-	✔	-	-	-	-
Torsades de pointes	-	<2	-	-	-	-	-	-
Ventricular tachycardia	-	<2	-	-	-	-	-	-
Central Nervous System								
Agitation	✔	-	-	-	-	-	-	-
Amnesia	-	-	-	-	-	-	-	2

Adverse Events	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Anxiety	-	-	1 to 3	-	-	-	-	-
Cerebral edema	✔	-	-	-	-	-	-	<1
Cerebral hemorrhage	-	-	<1	-	-	-	<1	<1
Cerebral infarction/ischemia	-	<2	-	-	-	-	-	-
Coma	✔	-	-	-	-	-	-	<1
Confusion	✔	-	<1	-	-	-	-	1
Delirium	✔	-	-	-	-	-	-	-
Depression	-	-	4	-	-	-	-	-
Dizziness	✔	9 to 10	2 to 6	14	4	4.5	-	-
Extremity pain	-	-	-	-	3	-	-	-
Fatigue	✔	-	3	-	4	3.2	-	6
Fever	-	-	1 to 3	-	5	-	-	-
Flushing	-	-	-	✔		-	-	-
Hallucination	-	<1	-	-		-	-	-
Headache	✔	27 to 34	3 to 8	2	2	6.5	-	38
Hyperthermia	✔	-	-	-	-	-	-	-
Insomnia	✔	-	1 to 3	-	-	-	-	-
Ischemic brain infarction	✔	-	-	-	-	-	-	-
Lethargy/malaise	✔	-	-	✔	-	-	-	2
Nervousness	✔	-	-	-	-	-	-	-
Pain	-	-	6	-	-	-	-	6
Seizure	-	-	-	-	-	-	-	2
Somnolence	-	-	-	-	-	-	-	1
Subdural hematoma	-	<2	-	-	-	-	-	-
Vertigo	-	<3	1 to 3	-	-	-	-	-
Dermatologic								
Alopecia	-	-	-	✔	-	-	-	<1
Angioedema	✔	-	-	-	-	-	-	-
Bullous eruption	-	-	<1	-	-	-	-	-
Eczema	-	-	1 to 3	-	-	-	-	-
Erythema multiforme	-	-	<1	-	-	-	<1	-
Erythema nodosum	-	-	-	-	-	-	<1	-
Exfoliative dermatitis	-	-	-	-	-	-	<1	-
Extradural hematoma	-	<2	-	-	-	-	-	-
Ischemic necrosis	-	-	<1	-	-	-	-	-

Adverse Events	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Lichen planus	-	-	<1	-	-	-	-	-
Maculopapular rash	-	-	<1	-	-	-	<1	-
Purpura	-	-	-	-	-	-	2	1
Pruritus	-	-	3	✔	-	-	1	<1
Rash	✔	-	4	2	3	-	5	<1
Stevens-Johnson syndrome	-	<2	-	-	-	-	<1	-
Toxic epidermal necrolysis	-	-	<1	-	-	-	-	-
Ulceration	-	-	-	-	-	-	-	<1
Urticaria	✔	-	<1	-	-	-	<1	<1
Endocrine and Metabolic								
Acidosis	✔	-	-	-	-	-	-	-
Dehydration	✔	-	-	-	-	-	-	-
Diabetes mellitus	-	<2	-	-	-	-	-	-
Gout/hyperuricemia	-	<2	1 to 3	-	-	-	-	-
Hypercholesterolemia	-	4	-	-	7	-	>10	-
Hyperglycemia	✔	-	-	-	-	-	-	-
Hyperkalemia	✔	-	-	-	-	-	-	-
Hypoglycemia	✔	-	-	-	-	-	-	-
Hyponatremia	✔	-	-	-	-	-	<1	-
Pancreatitis	-	-	<1	-	-	-	-	<1
Gastrointestinal								
Abdominal distress	-	-	-	6	-	-	-	-
Abdominal pain	✔	4 to 5	2 to 6	-	-	-	4	18
Abnormal stools	-	12 to 15	-	-	-	-	1	-
Anorexia	-	-	-	-	-	-	-	1
Bleeding	-	-	-	-	-	-	-	4
Chronic diarrhea	-	-	-	-	-	-	<1	-
Colitis	✔	<2	-	-	-	-	-	-
Colonic ulceration	✔	-	-	-	-	-	-	-
Constipation	-	-	1 to 3	-	-	-	-	-
Diarrhea	-	12 to 19	2 to 5	✔	-	3.7	13	13
Duodenal ulcer	✔	<2	-	-	2	-	-	-
Duodenitis	-	<2	-	-	-	-	-	-
Dyspepsia	✔	6	2 to 5	✔	-	-	7	>10
Epigastric discomfort/heartburn	✔	-	-	-	-	-	-	-

Adverse Events	**Single Entity Agents**							**Combination Products**
	Aspirin	**Cilostazol**	**Clopidogrel**	**Dipyridamole**	**Prasugrel**	**Ticagrelor**	**Ticlopidine**	**Aspirin and Dipyridamole**
Esophageal hemorrhage	-	<2	-	-	-	-	-	-
Esophageal stricture	✔	-	-	-	-	-	-	-
Esophageal ulcer	✔	-	-	-	-	-	-	-
Esophagitis	✔	<2	-	-	-	-	-	-
Flatulence	-	2 to 3	-	-	-	-	2	-
Gastric erosions	✔	-	-	-	-	-	-	-
Gastric erythema	✔	-	-	-	-	-	-	-
Gastrointestinal hemorrhage	-	-	1 to 3	-	2	-	<1	1
Hematemesis	-	-	-	-	-	-	-	<1
Hemorrhoids	-	-	-	-	-	-	-	1
Nausea	✔	6 to 7	3	✔	5	4.3	7	16
Oral mucosal ulcers	✔	-	-	-	-	-	-	-
Peptic ulcer	6 to 31	<2	-	-	-	-	<1	-
Periodontal abscess	-	<2	-	-	-	-	-	-
Rectal bleeding	-	<2	-	-	-	-	-	2
Rectal stenosis	✔	-	-	-	-	-	-	-
Retroperitoneal hemorrhage	-	<2	<1	-	-	-	-	-
Vomiting	✔	-	1 to 3	✔	-	-	2	8
Genitourinary					-			
Blood urea nitrogen increased	✔	-	-	-	-	-	-	-
Cystitis	-	<2	1 to 3	-	-	-	-	-
Hematuria	-	-	<1	-	-	-	<1	-
Interstitial nephritis	✔	-	-	-	-	-	-	<1
Menorrhagia	-	-	-	-	-	-	<1	-
Papillary necrosis	✔	-	-	-	-	-	-	<1
Proteinuria	✔	-	-	-	-	-	-	-
Renal failure	✔	-	-	-	-	-	<1	<1
Serum creatinine increased	✔	-	-	-	-	-	<1	-
Urinary tract infection	-	-	3	-	-	-	-	-
Uterine hemorrhage	-	-	-	-	-	-	-	<1
Hematologic								
Agranulocytosis	-	<2	<1	-	-	-	<1	-
Anemia	✔	<2	1 to 3	-	2	-	-	2
Aplastic anemia	-	-	<1	-	-	-	<1	<1
Bleeding	✔	-	4 to 5	-	-	8.7*, 85.8†	-	-

Adverse Events	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Coagulopathy	✔	-	-	-	-	-	-	-
Disseminated intravascular coagulation	✔	-	-	-	-	-	-	<1
Eosinophilia	-	-	-	-	-	-	<1	-
Epistaxis	-	-	3	-	-	-	-	-
Granulocytopenia	-	<2	<1	-	-	-	-	-
Hematoma	-	-	1 to 3	-	✔	-	-	-
Hemolytic anemia	✔	-	-	-	-	-	<1	-
Hemorrhage	-	<2	-	-	✔	-	-	-
Hypochromic anemia	-	-	<1	-	-	-	-	-
Iron deficiency anemia	✔	-	-	-	-	-	-	-
Leukopenia	-	<2	<1	-	3	-	-	-
Neutropenia	-	-	<1	-	-	-	2	-
Pancytopenia	-	-	<1	-	-	-	<1	<1
Polycythemia	-	<2	-	-	-	-	-	-
Prothrombin time prolonged	✔	-	-	-	-	-	-	<1
Purpura	-	-	5	-	-	-	-	-
Thrombocytopenia	✔	<2	<1	✔	✔	-	<1	<1
Thrombocytosis	-	-	-	-	-	-	<1	-
Thrombosis	-	<2	-	-	-	-	-	-
Thrombotic thrombocytopenic purpura	-	-	-	-	-	-	<1	-
Hepatic								
Acute liver failure	-	-	<1	-	-	-	-	-
Bilirubinemia	-	-	<1	-	-	-	-	-
Cholelithiasis	-	<2	-	✔	-	-	-	<1
Fatty liver	-	-	<1	-	-	-	-	-
Hepatic dysfunction	-	<2	-	-	✔	-	-	-
Hepatic failure	-	-	-	-	-	-	-	<1
Hepatic necrosis	-	-	-	-	-	-	<1	-
Hepatitis	✔	-	<1	✔	-	-	<1	<1
Hepatotoxicity	✔	-	-	-	-	-	-	-
Jaundice	✔	-	-	-	-	-	<1	<1
Liver dysfunction	-	-	-	✔	-	-	-	-
Liver function test abnormalities	-	-	<3	-	-	-	1	-
Transaminases increased	✔	-	-	-	-	-	-	-
Musculoskeletal								

Adverse Events	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Acetabular bone destruction	✔	-	-	-	-	-	-	-
Arthralgia	-	-	6	-	-	-	-	6
Arthritis	-	-	1 to 3	✔	-	-	-	2
Arthropathy	-	-	-	-	-	-	<1	-
Arthrosis	-	-	-	-	-	-	-	1
Back pain	-	6 to 7	6	-	5	3.6	-	5
Bursitis	-	<2	-	-	-	-	-	-
Fatigue	-	-	-	✔	-	-	-	-
Leg cramps	-	-	1 to 3	-	-	-	-	-
Myalgia	-	2 to 3	-	✔	-	-	-	1
Myositis	-	-	-	-	-	-	<1	-
Neuralgia	-	<2	1 to 3	-	-	-	-	-
Paresthesia	-	-	1 to 3	✔	-	-	-	<1
Peripheral neuropathy	-	-	-	-	-	-	<1	-
Rhabdomyolysis	✔	-	-	-	-	-	-	<1
Weakness	✔	-	1 to 3	-	-	-	-	2
Respiratory								
Asthma	✔	<2	-	-	-	-	-	-
Bronchiolitis obliterans	-	-	-	-	-	-	<1	-
Bronchitis	-	-	4	-	-	-	-	-
Bronchospasm	✔	-	-	-	-	-	-	<1
Cough	-	3 to 4	3	-	4	4.9	-	2
Dyspnea	✔	-	5	-	5	13.8	-	<1
Epistaxis	-	-	-	-	6	-	-	2
Hemoptysis	-	-	<1	-	-	-	-	<1
Hemothorax	-	-	<1	-	-	-	-	-
Hyperpnea	✔	-	-	-	-	-	-	-
Intestinal pneumonitis	-	-	<1	-	-	-	-	-
Larynx edema	✔	-	-	✔	-	-	-	-
Pharyngitis	-	7 to 10	-	-	-	-	-	-
Pneumonia	-	<2	-	-	-	-	-	-
Pneumonitis	-	-	-	-	-	-	<1	-
Pulmonary edema	✔	-	-	-	-	-	-	<1
Pulmonary hemorrhage	-	-	<1	-	-	-	-	-
Respiratory alkalosis	✔	-	-	-	-	-	-	-

Adverse Events	Single Entity Agents							Combination Products
	Aspirin	Cilostazol	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin and Dipyridamole
Rhinitis	-	7 to 12	4	-	-	-	-	-
Rhinosinusitis	✔	-	-	-	-	-	-	-
Tachypnea	✔	-	-	-	-	-	-	<1
Upper respiratory infection	-	-	-	-	-	-	-	1
Other								
Allergic reaction	-	-	<1	-	✔	-	-	<1
Anaphylactoid reaction/anaphylaxis	-	-	<1	-	-	-	<1	<1
Angioedema	-	-	<1	-	✔	-	<1	<1
Ante-/peri-/postpartum bleeding	✔	-	-	-	-	-	-	<1
Blindness	-	<2	-	-	-	-	-	-
Cataract	-	-	1 to 3	-	-	-	-	-
Conjunctival bleeding	-	-	-	-	-	-	<1	-
Conjunctivitis	-	-	1 to 3	-	-	-	-	-
Deafness	-	-	-	-	-	-	-	<1
Fever	-	-	<1	-	-	-	-	-
Flu symptoms	-	-	8	-	-	-	-	-
Hypersensitivity reaction	-	-	<1	✔	-	-	-	-
Infection	-	10 to 14	-	-	-	-	-	-
Lower weight infants	✔	-	-	-	-	-	-	<1
Noncardiac chest pain	-	-	-	-	-	3.7	-	-
Ocular/retinal hemorrhage	-	<2	<1	-	-	-	-	-
Periorbital edema	✔	-	-	-	-	-	-	-
Positive antinuclear antibody	-	-	-	-	-	-	<1	-
Prolonged pregnancy and labor	✔	-	-	-	-	-	-	-
Reye's syndrome	✔	-	-	-	-	-	-	<1
Sepsis	-	-	-	-	-	-	<1	-
Serum sickness	-	-	<1	-	-	-	<1	-
Stillbirths	✔	-	-	-	-	-	-	<1
Systemic lupus erythematosus	-	-	-	-	-	-	<1	-
Tinnitus	✔	-	-	-	-	-	-	-
Vasculitis	-	-	<1	-	-	-	<1	-

✔ Percent not specified.
- Event not reported.
*Non-coronary artery bypass graft-related bleeding.
†Coronary artier bypass graft-related bleeding.

Table 7. Boxed Warning for Cilostazol[1]

WARNING
Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. Cilostazol is contraindicated in patients with congestive heart failure of any severity.

Table 8. Boxed Warning for Clopidogrel[1]

WARNING
The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 system (CYP), primarily CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used an as aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

Table 9. Boxed Warning for Prasugrel[1]

WARNING
Prasugrel can cause significant, sometimes fatal, bleeding. Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients 75 years of age and older, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior myocardial infarction) in which its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery. When possible, discontinue prasugrel at least seven days prior to any surgery. Additional risk factors for bleeding include body weight less than 60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention, coronary artery bypass grafting, or other surgical procedures in the setting of prasugrel. If possible, manage bleeding without discontinuing prasugrel. Discontinuing prasugrel, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.

Table 10. Boxed Warning for Ticagrelor[1]

WARNING
Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding. Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage. Do not initiate therapy with ticagrelor in patients planning to undergo urgent coronary artery bypass graft (CABG) surgery. When possible, discontinue ticagrelor at least five days prior to any surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention, CABG, or other surgical procedures in the setting of ticagrelor. If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events. Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor; avoid such doses. After any initial dose, use with aspirin 75 to 100 mg/day.

Table 11. Boxed Warning for Ticlopidine[1]

WARNING
Ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura (TTP) and aplastic anemia. Neutropenia/Agranulocytosis: Among 2,048 patients in clinical trials in stroke patients, there were 50 cases (2.4%) of neutropenia (less than 1,200 neutrophils/mm^3), and the neutrophil count was below 450/mm^3 in 17 of these patients (0.8% of the total population). TTP: One case of thrombotic thrombocytopenic purpura was reported during clinical trials in stroke patients. Based on postmarketing data, United States physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated TTP may be as high as one case in every 2,000 to 4,000 patients exposed. Aplastic Anemia: Aplastic anemia was not seen during clinical trials in stroke patients, but US physicians reported about 50 cases between 1992 and 1998. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated aplastic anemia may be as high as one case in every 4,000 to 8,000 patients exposed. Monitoring of Clinical and Hematologic Status: Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks. The incidence of aplastic anemia peaks after about 4 to 8 weeks of therapy. The incidence of the hematologic adverse reactions declines thereafter. Only a few cases of neutropenia, TTP, or aplastic anemia have arisen after more than 3 months of therapy. Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first 3 months of treatment, patients receiving ticlopidine must, therefore, be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, ticlopidine should be immediately discontinued.

VII. Dosing and Administration

The usual dosing regimens for the platelet-aggregation inhibitors are listed in Table 12.

Table 12. Usual Dosing Regimens for the Platelet-Aggregation Inhibitors[1,3-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Aspirin	<u>Acute myocardial infarction:</u> Initial, 160 to 325 mg as soon as myocardial infarction is suspected; maintenance, 160 to 325 mg/day for 30 days, after 30 days consider further therapy based on dosage and administration for prevention of recurrent myocardial infarction <u>Analgesic/antipyretic:</u> Delayed-release tablet: initial, 1,300 mg; maintenance, 650 to 1,300 mg every eight hours; maximum, 3,900 mg per 24 hours or as directed by a	<u>Analgesic/antipyretic in children <12 years of age:</u> Tab let: 10 to 15 mg/kg/dose every four hours; maximum, up to 60 to 80 mg/kg/day <u>Analgesic/antipyretic in children ≥12 years of age:</u> Delayed-release tablet: initial, 1,300 mg; maintenance, 650 to 1,300 mg every eight hours; maximum, 3,900 mg per 24 hours or as directed by a healthcare professional	Chewable tablet: 81 mg Delayed-release Tablet: 81 mg 325 mg Packet: 650 mg Rectal suppository: 300 mg 600 mg Tablet: 325 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	healthcare professional Tablet: maintenance, 324 to 1,000 mg every four to six hours as needed; maximum, 4,000 mg per 24 hours or as directed by a healthcare professional <u>Arthritis and pleurisy of systemic lupus erythematosus:</u> Maintenance, 3 g/day in divided doses <u>Cartoid endarterectomy:</u> Maintenance, 80 mg once daily to 650 mg twice daily initiated presurgery ; continue therapy indefinitely <u>Chronic stable angina pectoris:</u> Maintenance, 75 to 325 mg once daily; continue therapy indefinitely <u>Coronary artery bypass graft:</u> Maintenance, 325 mg/day started six hours postprocedure; continue therapy for one year postprocedure <u>Ischemic stroke and transient ischemic attack:</u> Maintenance, 50 to 325 mg once daily; continue therapy indefinitely <u>Myocardial infarction, prophylaxis:</u> 75 to 325 mg once daily; continue therapy indefinitely <u>Osteoarthritis:</u> Maintenance, up to 3 g/day in divided doses <u>Percutaneous transluminal coronary angioplasty:</u> Initial, 325 mg two hours presurgery; maintenance, 160 to 325 mg/day; continue therapy indefinitely <u>Rheumatoid arthritis:</u> Initial, 3 g/day in divided	Tablet: maintenance, 324 to 1,000 mg every four to six hours as needed; maximum, 4,000 mg per 24 hours or as directed by a healthcare professional <u>Juvenile rheumatoid arthritis:</u> Tablet: initial, 90 to 130 mg/kg/day in divided doses	

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	doses <u>Spondyloarthropathies:</u> Maintenance, up to 4 g/day in divided doses <u>Unstable angina pectoris:</u> Maintenance, 75 to 325 mg once daily; continue therapy indefinitely		
Cilostazol	<u>Intermittent claudication:</u> Tablet: 100 mg orally twice daily	Safety and efficacy in children have not been established.	Tablet: 50 mg 100 mg
Clopidogrel	<u>Acute coronary syndrome, non-ST-segment elevation (unstable angina/non-Q-wave myocardial infarction):</u> Tablet: initial, 300 mg once; maintenance, 75 mg orally once daily, administered in combination with aspirin (75 to 325 mg once daily) <u>Acute coronary syndrome, ST-segment elevation acute myocardial infarction:</u> Tablet: 75 mg once daily, administered in combination with aspirin (75 to 325 mg once daily), with or without thrombolytics; clopidogrel may be initiated with or without a loading dose <u>Recent myocardial infarction, recent stroke, or established peripheral arterial disease:</u> Tablet: 75 mg once daily	Safety and efficacy in children have not been established.	Tablet: 75 mg 300 mg
Dipyridamole	<u>Cardiac valve replacement, adjunct prophylaxis:</u> Tablet: 75 to 100 mg four times daily as an adjunct to warfarin therapy <u>Radionuclide myocardial perfusion study:</u> Injection: 0.142 mg/kg/min (0.57 mg/kg total) intravenously over 4 minutes prior to thallium; maximum 60 mg	Safety and efficacy in children below the age of 12 years have not been established.	Injection: 5 mg/mL Tablet: 25 mg 50 mg 75 mg
Prasugrel	<u>Acute coronary syndrome:</u> Tablet: initial, 60 mg once; maintenance, 10 mg once daily (consider 5 mg once daily for patients <60 kg),	Safety and efficacy in children have not been established.	Tablet : 5mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	administered with aspirin (75 to 325 mg)		
Ticagrelor	<u>Acute coronary syndrome:</u> Tablet: initial, 180 mg once; maintenance, 90 mg twice daily, administered with aspirin (75 to 100 mg)*	Safety and efficacy in children have not been established.	Tablet : 90 mg
Ticlopidine	<u>Coronary artery stent implantation, adjunct:</u> Tablet: 250 mg twice daily together with antiplatelet doses of aspirin for up to 30 days of therapy following successful stent implantation <u>Stroke:</u> Tablet: 250 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 250 mg
Combination Products			
Aspirin and dipyridamole	<u>Thromboembolic stroke, recurrent, prophylaxis:</u> Capsule: 25-200 mg twice daily Alternative regimen for patients with intolerable headaches: 25-200 mg at bedtime and low-dose aspirin in the morning; return to usual dose as soon as tolerance to headache develops (usually within a week)	Safety and efficacy in children have not been established.	Capsule (IR aspirin-ER dipyridamole): 25-200 mg

*After the initial loading dose of aspiring (usually 325 mg), use ticagrelor with a daily maintenance dose of aspirin 75 to 100 mg.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the platelet-aggregation inhibitors are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Platelet-Aggregation Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cerebrovascular Conditions				
International Stroke Trial[30] (1997) Aspirin 300 mg/day vs heparin 5,000 or 12,500 IU BID vs aspirin and heparin vs placebo	MC, OL, RCT Patients with acute ischemic stroke (randomized within 48 hours of stroke onset), 61% of patients were >70 years	N=19,435 Up to 14 days	Primary: Death from any cause within 14 days, death or dependency at six months Secondary: Symptomatic intracranial or extracranial hemorrhage, ischemic stroke or other major event within 14 days	Primary: Aspirin-allocated patients experienced slightly fewer deaths within 14 days (9.0 vs 9.4%; P value not significant). There was a trend toward a reduction in death or dependence at six months (62.2 vs 63.5%; P=0.07; a difference of 13 per 1,000 patients) and after adjustment for baseline prognosis the benefit from aspirin was significant (P=0.03; a difference of 14 per 1,000 patients). More aspirin-allocated patients reported complete recovery from their stroke (17.6 vs 16.6%; P=0.07). Secondary: Aspirin-allocated patients had significantly fewer recurrent ischemic strokes within 14 days (2.8 vs 3.9%; P<0.001) with no significant excess of hemorrhagic strokes (0.9 vs 0.8%), so the reduction in death or nonfatal recurrent stroke with aspirin was significant (11.3 vs 12.4%; P=0.02; 11 fewer per 1,000 patients treated). Aspirin was associated with a significant excess of 5 transfused or fatal extracranial bleeds per 1,000 patients (1.1 vs 0.6%; P=0.0004), in the absence of heparin the excess was two and was not significant. There was no interaction between aspirin and heparin in the main outcomes.
CAST[31] (1997) Aspirin 160 mg/day vs	MC, PC, RCT Hospitalized patients with acute ischemic stroke (were randomized within 48 hours of stroke	N=21,106 Up to 4 weeks	Primary: Death from any cause during the four week treatment period, death or dependence at	Primary: Patients in the aspirin group experienced a small but significant reduction in both early mortality (3.3 vs 3.9%; P=0.04) and recurrent ischemic strokes (1.6 vs 2.1%; P=0.01) but slightly more hemorrhagic strokes than placebo (1.1 vs 0.9%; P>0.1). At discharge, the aspirin-treated group experienced a smaller proportion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	onset), mean age 63 years		discharge Secondary: Fatal or nonfatal recurrent stroke, death or nonfatal stroke during the scheduled treatment period	patients who were dead or dependent (30.5 vs 31.6%; P=0.08), corresponding to 11.4 fewer per 1,000 patients. Secondary: Fatal and nonfatal recurrent strokes occurred in 3.2% of aspirin-allocated patients vs 3.4% for placebo (P value not significant). For the combined in hospital end point of death or nonfatal stroke at 4 weeks, there was a 12% proportional risk reduction with aspirin (5.3 vs 5.9%; P=0.03), an absolute difference of 6.8 fewer cases per 1,000 patients.
Diener et al.[32] (1996) ESPS 2 Aspirin 25 mg BID vs aspirin and dipyridamole ER 25-200 mg BID (Aggrenox®) vs dipyridamole ER* 200 mg BID vs placebo	DB, MC, PC, RCT Male and female patients who had an ischemic stroke (76%) or TIA (24%) within 3 months prior to study entry, mean age 66.7 years	N=6,602 24 months	Primary: Stroke (fatal or nonfatal), death (all-cause mortality), combined stroke or death Secondary: TIA, adverse events	Primary: In comparison to placebo, stroke risk was reduced by 18% with aspirin alone (P=0.013), 37% with the fixed-dose combination product of aspirin and ER dipyridamole (P<0.001) and 16% with dipyridamole alone (P=0.039). There was no significant difference in all-cause mortality among the active treatment groups. In comparison to placebo, the risk of stroke or death was reduced by 13% with aspirin alone (P=0.016), 24% with the fixed-dose combination (P<0.001) and 15% with dipyridamole alone (P=0.015). Secondary: Aspirin alone (P<0.001), the fixed-dose combination product (P<0.001) and dipyridamole alone (P<0.01) were significantly effective in preventing TIA compared to placebo. Headache was the most common adverse event, occurring more frequently in the dipyridamole-treated patients. All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received aspirin in comparison to placebo or dipyridamole.
Leonardi-Bee et al.[33] (2005)	MA (5 trials) Patients with previous ischemic	N=11,036 15 to 72 months	Primary: Incidence of combined fatal and nonfatal stroke	Primary: The incidence of recurrent stroke was reduced by dipyridamole as compared to control (OR, 0.82; 95% CI, 0.68 to 1.00; P<0.05), and by combined aspirin and dipyridamole vs aspirin alone (OR, 0.78; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aspirin and dipyridamole vs dipyridamole vs aspirin vs control Two formulations of dipyridamole were assessed: conventional (daily dose 150 to 300 mg) and modified release (daily dose 400 mg). The daily dose of aspirin was 50 to 1,300 mg.	stroke and/or TIA		Secondary: Nonfatal stroke; combined fatal and nonfatal MI; vascular death; composite of nonfatal stroke, nonfatal MI and vascular death	0.65 to 0.93; P<0.05), dipyridamole alone (OR, 0.74; 95% CI, 0.60 to 0.90; P<0.05), or control (OR, 0.61; 95% CI, 0.51 to 0.71; P<0.05). Secondary: The combination of dipyridamole and aspirin also significantly reduced the composite outcome of nonfatal stroke, nonfatal MI, and vascular death as compared to aspirin alone (OR, 0.84; 95% CI, 0.72 to 0.97; P<0.05), dipyridamole alone (OR, 0.76; 95% CI, 0.64 to 0.90; P<0.05), or control (OR, 0.66; 95% CI, 0.57 to 0.75; P<0.05). The combination of dipyridamole and aspirin significantly reduced the incidence of fatal and nonfatal MI compared to control (P<0.05) but not compared to monotherapy with aspirin or dipyridamole (P>0.05). Vascular death was not altered in any group.
Sacco et al.[34] (2005) Aspirin and dipyridamole ER 25-200 mg BID (Aggrenox®) vs aspirin 25 mg BID	DB, MC, PC, RCT (Post-hoc analysis of the ESPS 2 trial) Male and female patients who had an ischemic stroke (76%) or TIA (24%) within 3 months prior to study entry, mean age 66.7 years	N=1,650 (Aggrenox®) N=1,649 (aspirin) Duration not specified	Primary: Rates of annual strokes and combined strokes and vascular events Secondary: Not reported	Primary: Compared to aspirin alone, aspirin plus ER dipyridamole was more effective in reducing the risk of stroke (relative risk reduction, 23%; P=0.006) and stroke or vascular events (relative risk reduction, 22%, P=0.003). A more pronounced efficacy was observed for patients <70 years; those with hypertension, prior MI, prior stroke or TIA, and any prior cardiovascular disease; and smokers (P<0.01 for all). The greatest relative hazard reduction (44.6%) was noted for patients with a stroke or TIA before the qualifying event.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significant hazard reductions were reported for the combined outcome of stroke or vascular events with the greatest reductions found in patients with prior stroke or TIA, previous MI and among current smokers. The difference in efficacy increased in higher-risk patients. Secondary: Not reported
ESPRIT Study Group[35] (2006) ESPRIT Aspirin (30 to 325 mg/day) and dipyridamole ER (200 mg BID), either as a fixed-dose combination or individual components vs aspirin 30 to 325 mg/day	MC, OL, RCT Patients with a TIA or minor stroke	N=2,739 3.5 years (mean follow-up)	Primary: Composite of death from all vascular causes, nonfatal stroke, nonfatal MI or major bleeding complication (whichever happened first) Secondary: Death from all causes, death from all vascular causes, death from all vascular causes and nonfatal stroke, all major ischemic events, all vascular events, major bleeding complications	Primary: Primary outcome events occurred in 173 (13%) of patients on aspirin plus dipyridamole vs 216 (16%) on aspirin monotherapy (HR, 0.80; 95% CI, 0.66 to 0.98; absolute risk reduction, 1.0% per year; 95% CI, 0.1 to 1.8). Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs 184), mainly because of headache. Secondary: The HRs for death from all causes and all vascular causes were 0.88 (95% CI, 0.67 to 1.17) and 0.75 (95% CI, 0.51 to 1.10). Ischemic events were less frequent in the combination group than in the monotherapy group (HR, 0.81; 95% CI, 0.65 to 1.01). Major bleeding complications arose in 35 patients allocated to aspirin and dipyridamole vs 53 patients allocated to aspirin alone, whereas minor bleeding was reported in 171 patients allocated to the combination regimen vs 168 patients allocated to aspirin (RR, 1.03; 95% CI, 0.84 to 1.25).
Uchiyama et al. (2011)[36] JASAP Aspirin and dipyridamole ER 25 to 200 mg BID	AC, DB, MC, PG, RCT Patients ≥50 years of age with an ischemic stroke ≥1 week (but no more than 6	N=1,294 12 months	Primary: Recurrent ischemic stroke (fatal or nonfatal) Secondary: Cerebral	Primary: Recurrent ischemic stroke occurred in 6.9 (n=45) and 5.0% (n=32) of patients receiving combination therapy and aspirin, respectively. Noninferiority of combination therapy compared to aspirin was not shown (HR, 1.47; 95% CI, 0.93 to 2.31). Results were consistent in the per protocol population.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 81 mg QD Concomitant use of anticoagulation and antiplatelet therapies was prohibited.	months) prior to enrollment, with ≥2 additional risk factors, stable neurological signs and symptoms, and responsible lesion confirmed by CT or MRI		hemorrhage; subarachnoid hemorrhage; TIA; ACS; other vascular events; composite of ischemic stroke, TIA, MI, unstable angina, or sudden death attributable to thromboembolism; stroke (composite of ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage); safety A post hoc analysis was performed evaluating the event rate of intracranial hemorrhage and the composite of stroke or major bleeding for different subgroups	Secondary: The event rate of stroke was significantly higher with combination therapy compared to aspirin. There was no difference between the two treatments for any other secondary endpoint. Combination therapy and aspirin were both well tolerated. There was a significantly higher total number of adverse events with combination therapy (640 vs 611; P=0.04). The difference in drug-related adverse events was mainly due to headache in the early stages of treatment with combination therapy. More patients receiving combination therapy discontinued treatment because of headache. Major bleeding events and clinically relevant minor bleeding events were comparable between the two treatments. No relevant changes in laboratory parameters, vital signs, and electrocardiography were noted with either treatment. There were four (0.6%) and 10 (1.6%) deaths with combination therapy and aspirin. A multivariate analysis taking into account potential confounders for recurrence of ischemic stroke but only keeping covariates with a significant contribution in the model revealed a similar result for the comparison between treatments as the primary analysis. The analysis also revealed that higher modified Rankin Scale values and established end organ damage at baseline had a deleterious effect on the primary outcome, whereas the concomitant therapy with statins had a beneficial effect.
Verro et al.[37] (2008) Aspirin and dipyridamole (IR and ER formulations)	MA (6 trials) Patients with a history of non-cardioembolic stroke or TIA	N=7,648 Duration varied	Primary: Incidence of nonfatal stroke Secondary: Composite of stroke, MI or	Primary: Dipyridamole plus aspirin significantly reduced the risk of nonfatal ischemic and hemorrhagic stroke compared to aspirin alone (RR, 0.77; 95% CI, 0.67 to 0.89). Secondary: Dipyridamole plus aspirin significantly reduced the risk of the composite

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin			vascular death, subset analysis comparing outcomes with IR and ER dipyridamole	of stroke, MI or vascular death (RR, 0.85; 95% CI, 0.76 to 0.94). Based on four trials, IR dipyridamole plus aspirin did not show a statistically significant reduction in the risk of stroke (RR, 0.83; 95% CI, 0.59 to 1.15) or the composite outcome (RR, 0.95; 95% CI, 0.75 to 1.19) compared to aspirin alone. Based on 2 trials (ESPS 2 and ESPRIT), ER dipyridamole plus aspirin showed a significant reduction in risk for stroke (RR, 0.76; 95% CI, 0.65 to 0.89) and for the composite outcome (RR, 0.82; 95% CI, 0.73 to 0.92) compared to aspirin alone.
Geeganage et al. (2012)[38] Dual therapy with clopidogrel or dipyridamole plus aspirin vs monotherapy with aspirin, clopidogrel or dipyridamole	MA (12 RCTs) Patients with acute ischemic stroke or TIA	N=3,766 Duration varied	Primary: Recurrent stroke Secondary: Composite of stroke, TIA, ACS and death; composite of nonfatal stroke, nonfatal MI and vascular death; MI, severe stroke, intracerebral hemorrhage, major bleeding, all-cause death and vascular death	Primary: Dual antiplatelet therapy was associated with a significant decrease in stroke recurrence in comparison to monotherapy (3.3 vs 5.0%; RR, 0.67; 95% CI, 0.49 to 0.93). Secondary: Compared to monotherapy, dual antiplatelet therapy was associated with a significant reduction in the risk of composite endpoint of stroke, TIA, ACS and death (1.7 vs 9.1%; RR, 0.71; 95% CI, 0.56 to 0.91) as well as the composite endpoint of nonfatal stroke, nonfatal MI and vascular death (4.4 vs 6.0%; RR, 0.75; 95% CI, 0.56 to 0.99). No significant differences were seen between dual therapy and monotherapy with regard to the occurrence of MI (RR, 0.71; 95% CI, 0.25 to 2.03), severe stroke (RR, 1.01; 95% CI, 0.91 to 1.12), intracerebral hemorrhage (RR, 1.39; 95% CI, 0.22 to 8.75), all-cause death (RR, 1.34; 95% CI, 0.76 to 2.34) and vascular death (RR, 1.31; 95% CI, 0.59 to 2.93). Major bleeding occurred more frequently with dual therapy compared to monotherapy, though this increase was not statistically significant (RR, 2.09; 95% CI, 0.86 to 5.06).
Sacco et al.[39] (2008) PROFESS Aspirin 25 mg and	DB, RCT Patients ≥55 years of age with a recent ischemic stroke	N=20,332 2.5 years	Primary: Recurrent stroke of any type Secondary:	Primary: Of those in the aspirin/dipyridamole group, 916 patients (9%) experienced a recurrent stroke compared to 898 patients (8.8%) in the clopidogrel group (HR, 1.01; 95% CI, 0.92 to 1.11).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dipyridamole ER 200 mg BID vs clopidogrel 75 mg QD	within 90 days of randomization		Composite of stroke, MI, or death from vascular causes	Secondary: Each group had 1,333 patients (13.1%) experience MI or death from a vascular cause (HR, 0.99; 95% CI, 0.92 to 1.07).
Markus et al.[40] (2005) CARESS Clopidogrel 300 mg on day 1, followed by 75 mg QD on days 2 to7 plus aspirin 75 mg QD vs aspirin 75 mg QD	DB, PC, RCT Patients with ≥50% carotid stenosis	N=107 7 days	Primary: Proportion of patients who were MES positive on day seven Secondary: Proportion of patients who were MES positive on day two, rate of embolization on both days two and seven and their percent change from baseline, safety	Primary: ITT analysis revealed a significant reduction in the primary end point: 43.8% of dual-therapy patients were MES positive on day seven, as compared to 72.7% of monotherapy patients (RR reduction, 39.8%; 95% CI, 13.8 to 58.0; P=0.0046). Secondary: MES frequency per hour was reduced compared to baseline by 61.4% (95% CI, 31.6 to 78.2; P=0.0013) in the dual-therapy group at day seven and by 61.6% (95% CI, 34.9 to 77.4; P=0.0005) on day two. There were four recurrent strokes and seven TIAs in the monotherapy group vs no stroke and four TIAs in the dual-therapy group that were considered treatment emergent and ipsilateral to the qualifying carotid stenosis. MES frequency was greater in the 17 patients with recurrent ipsilateral events compared to the 90 without (P=0.0003).
Diener et al.[41] (2004) MATCH Clopidogrel 75 mg/day vs clopidogrel 75 mg/day and aspirin 75 mg/day	DB, PC, RCT High-risk patients with recent ischemic stroke or TIA and had at least one additional vascular risk factor who were already receiving clopidogrel	N=7,599 18 months	Primary: Composite of ischemic stroke, MI, vascular death or rehospitalization for an acute ischemic event Secondary: Death, stroke, individual components and	Primary: There was no significant benefit of combination therapy compared to clopidogrel monotherapy in reducing the primary outcome (15.7 vs 16.7%, respectively; P=0.244). Secondary: There was no significant benefit of combination therapy compared to clopidogrel alone in reducing the secondary outcomes. Life-threatening bleedings were higher in the group receiving aspirin and clopidogrel vs clopidogrel monotherapy (2.6 vs 1.3%; P<0.0001). Major and minor bleeding were also significantly higher with combination

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			various combinations of the primary end points	therapy vs clopidogrel monotherapy (P<0.0001 for both).
Kennedy et al.[42] (2007) FASTER <u>Group 1</u> Clopidogrel 300 mg loading dose, followed by 75 mg QD vs placebo <u>Group 2</u> Simvastatin 40 mg QD vs placebo All patients were also given aspirin 81 mg QD with a 162 mg loading dose if naïve to aspirin.	DB, PC, RCT Patients ≥40 years of age with TIA or minor stroke	N=392 90 days	Primary: Incidence of stroke (ischemic and hemorrhagic), safety (hemorrhage, myositis) Secondary: Composite of stroke, MI and vascular death	Primary: The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrollment rate because of increased use of statins. Within 90 days, 7.1% of patients on clopidogrel had a stroke compared to 10.8% of patients on placebo (RR, 0.7; 95% CI, 0.3 to 1.2) for an absolute risk reduction of -3.8% (95% CI, -9.4 to 1.9; P=0.19). In the simvastatin group, 10.6% of patients had a stroke within 90 days compared to 7.3% of patients on placebo (RR, 1.3; 95% CI, 0.7 to 2.4) for an absolute risk increase of 3.3% (95% CI, -2.3 to 8.9; P=0.25). Two patients on clopidogrel had intracranial hemorrhage compared to none on placebo (absolute risk increase 1.0%; 95% CI, -0.4 to 2.4; P=0.5). There was no difference between groups for the simvastatin safety outcomes. Secondary: Clopidogrel was associated with a -3.3% risk difference in the secondary end point compared to placebo (95% CI, -9.3% to 2.7%; P=0.28). Simvastatin was associated with a 2.7% risk difference compared to placebo (95% CI, -3.2% to 8.7%; P=0.37).
Uchiyama et al.[43] (2009) Clopidogrel 75mg QD	DB, RCT Japanese men 20 to 80 years of age with a history of cerebral	N=1,869 26 weeks and 52 weeks	Primary: Safety Secondary: Combined efficacy	Primary: Significantly fewer patients experienced a safety event in the clopidogrel group than the ticlopidine group (P<0.001; HR, 0.610; 95% CI 0.529, 0.703).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ticlopidine 200 mg QD	infarctions		end point of cerebral infarction, MI, and vascular death	Almost twice as many patients in the ticlopidine group (25.6%) experienced hepatic dysfunction than in the clopidogrel group (13.4%). Secondary: There was no significant difference in the incidence of the combined efficacy endpoint between clopidogrel (2.6% of patients) and ticlopidine (2.5%). Clopidogrel was better tolerated than ticlopidine; there was no difference in the efficacy of the two products with regard to the secondary prevention of vascular events in patients with prior stroke.
Fukuuchi et al.[44] (2008) Ticlopidine 200 mg QD vs clopidogrel 75 mg QD	DB, DD, MC, RCT Japanese patients between the ages of 20 and 80 years who experienced a non-cardioembolic cerebral infarction ≥8 days prior to enrollment	N=1,151 52 weeks	Primary: Safety with emphasis on hematologic changes, hepatic dysfunction, nontraumatic hemorrhage and other serious adverse reactions Secondary: Combined incidence of nonfatal or fatal cerebral infarction or MI, or death due to other vascular causes	Primary: During the 52-week study period, 15.1% of ticlopidine patients and 7.0% of clopidogrel patients had at least one primary safety end point (P<0.001). Significant differences were primarily noted between ticlopidine and clopidogrel for hematologic disorders (2.4 vs 1.0%; P=0.043) and hepatic dysfunction (11.9 vs 4.2%; P<0.001). Study medication was discontinued prematurely due to safety end points in 27 and 17% of patients receiving ticlopidine and clopidogrel, respectively (P<0.001). The HR for the risk of discontinuing study medication due to a primary safety end point was 0.559 (95% CI, 0.434 to 0.721) in favor of clopidogrel. Secondary: The incidence of vascular events did not differ significantly between ticlopidine and clopidogrel (2.6 vs 3.0%, respectively; P=0.948; HR, 0.977; 95% CI, 0.448 to 1.957).
Gent et al.[45] (1989) CATS Ticlopidine 250 mg BID	DB, MC, PC, RCT Patients with ischemic strokes occurring from 1 week to 4 months	N=1,072 Up to 3 years	Primary: Event rate per year for stroke, MI, or vascular death Secondary: Adverse events	Primary: The event rate per year for stroke, MI or vascular death was 10.8% in the ticlopidine group and 15.3% in the placebo group. Compared to placebo, ticlopidine reduced the RR of stroke, MI or vascular death by 30% (P=0.006) in the on-treatment analysis and by 23% (P=0.020) using the intent-to-treat approach.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				Ticlopidine reduced the RR of ischemic stroke by 33% (P=0.008) in the on-treatment analysis. Ticlopidine was beneficial for both men and women (RR, 28.1%; P=0.037 and RR, 34.2%; P=0.045, respectively). Secondary: Adverse events associated with ticlopidine included neutropenia (severe in about 1% of cases), skin rash (severe 2%) and diarrhea (severe 2%).
Hass et al.[46] (1989) TASS Ticlopidine 250 mg BID vs aspirin 650 mg BID	Blinded, MC, RCT Patients with recent (within 3 months) minor stroke or TIA	N=3,069 2 to 6 years	Primary: Nonfatal stroke or death Secondary: Adverse events	Primary: Compared to aspirin, ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate was 17% for ticlopidine vs 19% for aspirin; P=0.048). Ticlopidine reduced the risk of stroke after 3 years by 21% (10% for ticlopidine vs 13% for aspirin; P=0.024). Secondary: Ticlopidine significantly increased total cholesterol compared to aspirin (9 vs 2%; P<0.01). Serious gastrointestinal adverse effects were 2.5 times more common in the aspirin group but bleeding from other anatomic sites was infrequent and about equal in the two treatment groups. Severe neutropenia occurred in 0.9% of patients.
Gorelick et al.[47] (2003) AAASPS Ticlopidine 250 mg BID vs aspirin 325 mg BID	DB, MC, RCT African American men and women who recently had a non-cardioembolic ischemic stroke	N=1,809 Up to 2 years	Primary: Composite of recurrent stroke, MI, or vascular death Secondary: Fatal or nonfatal stroke	Primary: There was no statistically significant difference in the percent of patients reaching the primary outcome of recurrent stroke, MI or vascular death between ticlopidine and aspirin (14.7 vs 12.3%, respectively; P=0.12). Secondary: There was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group (P=0.08). The frequency of laboratory-determined serious neutropenia was 3.4% for ticlopidine vs 2.2% for aspirin (P=0.12).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Combined Cardiovascular and Cerebrovascular Conditions				
Simpson et al.[48] (2011) Aspirin vs no aspirin therapy	MA (17 RCTs and 4 cohort trials) Trials evaluating the use of aspirin in diabetic patients for primary and/or secondary prevention	N=17,522 Duration varied	Primary All-cause mortality Secondary: Cardiovascular-related mortality, MI, stroke	Primary: Analysis of all-cause mortality was based on 1,172 (15.4%) deaths in 7,592 patients receiving aspirin and 1,520 (18.4%) deaths in 8,269 control patients. The pooled RR (25 trials) was 0.93 (95% CI, 0.81 to 1.07; P=0.31). Stratification according to daily aspirin dose did not reveal a significant dose-response relationship. Secondary: Cardiovascular mortality was reported in 447 (7.7%) of 5,798 of patients receiving aspirin and 599 (9.3%) of 6,456 of control patients. The pooled RR (16 trials) was 0.98 (95% CI, 0.76 to 1.25; P=0.86). An MI occurred in 547 (8.3%) of 6,605 patients receiving aspirin and 720 (10.0%) of control patients. The pooled RR (18 trials) was 0.84 (95% CI, 0.65 to 1.09; P=0.20). A stroke occurred in 344 (5.0%) of 6,902 patients receiving aspirin and 418 (5.6%) of 7,420 control patients. The pooled RR (21 trials) was 0.89 (95% CI, 0.892 to 1.16; P=0.80).
Antithrombotic Trialists' Collaboration.[49] (2002) Antiplatelet agents vs control vs one antiplatelet regimen vs another	MA (287 trials) Patients at high risk of occlusive vascular events	N=135,640 Duration varied	Primary: "Serious vascular event" (nonfatal MI, nonfatal stroke or vascular death) Secondary: Not reported	Primary: Overall, antiplatelet therapy reduced the combined outcome of any serious vascular event by 25%, nonfatal MI by 34%, nonfatal stroke by 25%, and vascular mortality by 15% with no apparent adverse effect on other deaths. Aspirin was the most widely studied antiplatelet drug and low dose (75 to 150 mg daily) was at least as effective as higher daily doses for long-term use. In acute settings an initial loading dose of at least 150 mg aspirin may be required. Clopidogrel reduced serious vascular event by 10% compared to aspirin, which was similar to the 12% reduction observed with ticlopidine. The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared to aspirin alone. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Sudlow et al.[50] (2009) Aspirin (325 mg/day for most studies) vs clopidogrel (75 mg QD for most studies) or ticlopidine (250 mg BID for most studies)	MA (10 trials) Patients at high risk for serious vascular events, including those with a previous TIA or ischemic stroke	N=26,865 Duration varied	Primary: Composite outcome of stroke, MI, or death from a vascular cause Secondary: Outcomes of adverse drug events	Primary: Treatment with clopidogrel or ticlopidine produced a modest reduction in the odds of a serious vascular event (11.6%) vs aspirin (12.5%; OR, 0.92; 95% CI, 0.85 to 0.99). This corresponds to the avoidance of 10 serious vascular events per 1,000 patients treated with clopidogrel or ticlopidine rather than aspirin for an average of about two years. Secondary: Compared to aspirin, clopidogrel and ticlopidine significantly reduced gastrointestinal adverse effects. However, clopidogrel and ticlopidine increased the odds of skin rash and diarrhea, ticlopidine more than clopidogrel. Allocation to ticlopidine, but not clopidogrel, significantly increased the odds of neutropenia.
CAPRIE Steering Committee[51] (1996) CAPRIE Clopidogrel 75 mg QD vs aspirin 325 QD	DB, MC, PG, RCT Patients with recent ischemic stroke (within 6 months with at least a week of residual neurological signs), recent MI (within 35 days) or symptomatic peripheral arterial disease	N=19,185 1 to 3 years	Primary: Composite outcome of ischemic stroke, MI or vascular death Secondary: Primary outcome and amputation, vascular death, all-cause mortality, safety	Primary: Intention–to-treat analysis showed that patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, MI, or vascular death compared to 5.83% with aspirin, for a RR reduction of 8.7% (95% CI, 0.3 to 16.5; P=0.043) in favor of clopidogrel. Corresponding on-treatment analysis yielded a RR reduction of 9.4% in favor of clopidogrel. For the 6,431 patients admitted to the study with prior stroke, the RR reduction for ischemic stroke, MI, or vascular death was 7.3% in favor of clopidogrel (P=0.26), and the RR reduction for the end point of stroke was 8.0% (P=0.28). For the 6,302 patients admitted to the study with myocardial infarction, an RR increase of 3.7% was associated with clopidogrel (P=0.66). For the 6,452 patients admitted to the study with peripheral arterial disease, an RR of 23.8% was noted in favor of clopidogrel (P=0.0028).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Clopidogrel reduced the risk of the primary outcome plus amputation by 7.6% compared to aspirin (P=0.076). There was no significant difference between clopidogrel and aspirin with regards to vascular death (1.90 vs 2.06%; P=0.29) and all-cause mortality (3.05 vs 3.11%; P=0.71). There were no major differences in terms of safety. Severe rash (P=0.017) and severe diarrhea (P=0.080) were reported more frequently with clopidogrel and severe upper gastrointestinal discomfort (P=0.096), intracranial hemorrhage (P=0.23) and gastrointestinal hemorrhage (P=0.05) were reported more frequently with aspirin.
Zhou et al.[52] (2012) Aspirin plus clopidogrel vs aspirin vs clopidogrel	MA, SR (7 RCTs) Trials evaluating the use of aspirin and/or clopidogrel patients for primary and/or secondary prevention	N=48,248 Duration varied	Primary: Major cardiovascular events Secondary: Not reported	Primary: Overall, with combination therapy the harm of major cardiovascular events was significantly reduced by 9% (RR, 0.91; 95% CI, 0.83 to 0.98) compared to monotherapy with aspirin and clopidogrel (six trials; n=46,132). Combination therapy resulted in a significant 14% reduction in the harm of MI compared to monotherapy with aspirin and clopidogrel (RR, 0.86; 95% CI, 0.76 to 0.97) (seven trials; n=48,248). Combination therapy resulted in a significant 16% reduction in the harm of stroke compared to monotherapy with aspirin and clopidogrel (RR, 0.84; 95% CI, 0.72 to 0.99) (seven trials; n=48,248). There was no evidence to show that combination therapy could reduce the risk of mortality, regardless of total mortality, vascular death, or non-vascular death compared to monotherapy aspirin and clopidogrel. There was no effect of combination therapy on the harm of revascularization events compared to monotherapy with aspirin and clopidogrel. Combination therapy significantly increased the harm of major bleeding events by 62% compared to monotherapy with aspirin and clopidogrel

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(RR, 1.62; 95% CI, 1.26 to 2.08) (seven trials; n=46,073). Secondary: Not reported
DeSchryver et al.[53] (2007) Dipyridamole with or without other antiplatelet drugs vs control (no drug or another antiplatelet drug)	MA (29 trials) Patients with arterial vascular disease (angina, CAD, MI, nephropathy, PAD, retinopathy, stroke and TIA)	N=23,019 Duration varied	Primary: Secondary prevention of vascular death and vascular events (defined as vascular death or any death from an unknown cause, nonfatal stroke or nonfatal MI) Secondary: Not reported	Primary: Compared to control, dipyridamole had no clear effect on vascular death (RR, 0.99; 95% CI, 0.87 to 1.12). The dose of dipyridamole or type of presenting vascular disease did not influence this result. Compared to control, dipyridamole appeared to reduce the risk of vascular events (RR, 0.88; 95% CI, 0.81 to 0.95). This effect was only statistically significant in patients presenting with cerebral ischemia. There was no evidence that dipyridamole alone was more efficacious than aspirin. Secondary: Not reported
Cardiovascular Conditions (Acute Coronary Syndrome, Myocardial Infarction, Angina Pectoris)				
CURE Trial Investigators[54] (2001) CURE Clopidogrel (300 mg immediately, followed by 75 mg QD) plus aspirin vs aspirin	DB, PC, RCT Patients with NSTEMI, presenting within 24 hours of symptom onset	N=12,562 3 to 12 months	Primary: Composite of death from cardiovascular causes, nonfatal MI, or stroke (first primary outcome); composite of the first primary outcome or refractory ischemia (second primary outcome) Secondary: Severe ischemia, heart failure, need for	Primary: A composite of death from cardiovascular causes, nonfatal MI, or stroke occurred in 9.3% of patients in the clopidogrel and aspirin group compared to 11.4% of patients in the aspirin group (RR, 0.80; 95% CI, 0.72 to 0.90; P<0.001). When refractory ischemia was included with the first primary outcome, the composite rate was 16.5% in the clopidogrel and aspirin group compared to 18.8% for aspirin alone (RR, 0.86; 95% CI, 0.79 to 0.94; P<0.001). Secondary: Significant reductions in nonfatal MI (5.2 vs 6.7%) and trends toward reduction in death (5.1 vs 5.5%) and stroke (1.2 vs 1.4%) with clopidogrel plus aspirin vs aspirin alone were noted. The percentages of patients with in hospital refractory or severe ischemia, recurrent angina, heart failure and revascularization procedures were also

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			revascularization, safety	significantly lower with clopidogrel plus aspirin vs aspirin alone (P<0.05 for all). There were significantly more patients with major bleeding in the clopidogrel plus aspirin group than in the aspirin group (3.7 vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; P=0.001), but there were not significantly more patients with episodes of life-threatening bleeding (2.1 vs 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56; P=0.13).
COMMIT Collaborative Group[55] (2005) COMMIT Clopidogrel 75 mg/day plus aspirin 162 mg/day vs aspirin 162 mg/day	MC, PC, RCT Patients admitted to the hospital within 24 hours of suspected acute MI, mean age 61 years	N=45,852 15 days (mean duration)	Primary: Composite of death, reinfarction or stroke; death from any cause Secondary: Safety	Primary: Allocation to clopidogrel plus aspirin produced a highly significant 9% proportional reduction in death, reinfarction or stroke compared to aspirin alone (actual reductions 9.2 vs 10.1%, respectively; P=0.002), corresponding to nine fewer events per 1,000 patients treated for about two weeks. There was also a significant 7% proportional reduction in any death in the clopidogrel plus aspirin group compared to aspirin alone (7.5 vs 8.1%; P=0.03). Secondary: Considering all fatal, transfused, or cerebral bleeds together, no significant excess risk was noted with clopidogrel plus aspirin vs aspirin alone, either overall (0.58 vs 0.55%, respectively; P=0.59) or in patients older than 70 years or in those given fibrinolytic therapy.
Sabatine et al.[56] (2005) CLARITY-TIMI 28 Clopidogrel 300 mg loading dose, followed by 75 mg QD plus aspirin vs aspirin	DB, MC, PC, RCT Patients 18 to 75 years of age who presented within 12 hours after the onset of an STEMI	N=3,491 30 days	Primary: Composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography (death or recurrent MI by day 8 or hospital discharge in patients who did not undergo	Primary: The primary end point was reached in 15.0% of patients receiving clopidogrel vs 21.7% for placebo, representing an absolute reduction of 6.7% in the rate and 36% in the odds of reaching the end point with clopidogrel therapy (95% CI, 27 to 47; P<0.001). By 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20% (from 14.1 to 11.6%; P=0.03). Secondary: The rates of major bleeding and intracranial hemorrhage were similar in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients received a fibrinolytic agent, and heparin when appropriate.			angiography) Secondary: Safety	the two groups.
Ahmed et al.[57] (2011) Clopidogrel 300 mg once, followed by 75 mg/day vs placebo Patients received a fibrinolytic agent, aspirin, and when appropriate, heparin.	Substudy of CLARITY-TIMI 28 trial Patients 18 to 75 years of age who presented within 12 hours after the onset of an STEMI stratified by baseline GFR	N=3,252 30 days (study medication given up to, and including, the day of angiography, or up to day 8 or hospital discharge if no angiography)	Primary: Composite of an occluded infarct-related artery on angiography, all-cause mortality or recurrent MI prior to angiography (death or recurrent MI by day eight or hospital discharge in patients who did not undergo angiography) Secondary: Composite clinical endpoint of cardiovascular death, MI, or recurrent ischemia leading to urgent revascularization at 30 days; cardiovascular death; safety	Primary: There was a significant trend for an increased rate of the primary composite endpoint with lower GFR and was the highest rate (23.4%) in patients with moderately reduced GFR (P=0.003). Secondary: By day 30, both the rates of the composite clinical endpoint (P<0.0001) and the safety endpoints of bleeding (P=0.0008) and intracranial hemorrhage (P=0.03) also trended towards a significant increase with lower GFRs. By day 30, there was a significant trend for an increased rate of cardiovascular death with lower GFR and was the highest rate (11.3%) in patients with moderately reduced GFR (P<0.0001).
Bhatt et al.[58] (2006) CHARISMA Clopidogrel 75 mg QD plus aspirin 75 to 162 mg QD	DB, MC, PC, RCT Patients 45 years of age or older with clinically evident cardiovascular disease (e.g.,	N=15,603 28 months	Primary: Composite of first occurrence of MI, stroke, or death from cardiovascular causes	Primary: The composite of MI, stroke or death from cardiovascular causes was 6.8% with clopidogrel plus aspirin and 7.3% with aspirin (RR, 0.93; 95% CI, 0.83 to 1.05; P=0.22). The rate of the primary end point among patients with multiple risk factors was 6.6% with clopidogrel plus aspirin and 5.5% with aspirin alone (RR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 75 to 162 mg QD	documented coronary, cerebrovascular or peripheral arterial disease) or multiple atherothrombotic risk factors		Secondary: First occurrence of MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	1.2; 95% CI, 0.91 to 1.59; P=0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel plus aspirin than aspirin alone (3.9 vs 2.2%; P=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel plus aspirin and 7.9% with aspirin alone (RR, 0.88; 95% CI, 0.77 to 1.00; P=0.046). Secondary: The secondary end point was reached in 16.7 and 17.9% (RR, 0.92; 95% CI, 0.86 to 1.00; P=0.04) of patients receiving clopidogrel plus aspirin vs aspirin alone, respectively. The rate of severe bleeding was 1.7 and 1.3% (RR, 1.25; 95% CI, 0.97 to 1.61; P=0.09) for patients receiving clopidogrel plus aspirin vs aspirin.
Dasgupta et al.[59] (2009) Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day vs aspirin 75 to 162 mg/day	Post hoc analysis of CHARISMA Post hoc analysis of patients with diabetic neuropathy in the CHARISMA trial, who were ≥45 years of age with clinically evident cardiovascular disease or multiple atherothrombotic risk factors	N=2,009 Median 28 months	Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes Secondary: First occurrence of MI, stroke, death from cardiovascular causes or hospitalization for unstable angina, TIA or revascularization procedure; safety	Primary: Almost all cardiovascular events occurred significantly more frequently in diabetic patients with neuropathy. Patients with diabetic neuropathy had a higher case fatality rate of MI compared to diabetic patients without nephropathy and nondiabetic patients (20 vs 14 vs 11%, respectively), but this higher rate was not significant (P=0.240). Secondary: Patients with nephropathy who were assigned clopidogrel experienced a significant increase in overall mortality (HR, 1.8; 95% CI, 1.2 to 2.7; P=0.006) compared to placebo, as well as significantly increased cardiovascular mortality (HR, 1.7; 95% CI, 1.1 to 2.9; P=0.028). The frequency of bleeding in patients with diabetic nephropathy who received clopidogrel tended to be higher compared to placebo, but this increase was not significant (2.6 vs 1.5%; HR, 1.8; P=0.075).
Hart et al.[60] (2008) CHARISMA Clopidogrel 75 mg	DB, MC, PC, RCT (Post hoc analysis of participants with a history of atrial fibrillation in the	N=593 28 months (median duration)	Primary: Composite of first occurrence of MI, stroke or death from	Primary: There was no difference in the composite of stroke, MI or vascular death between patients receiving clopidogrel plus aspirin (35 of 298 patients) and aspirin alone (27 of 285 patients; P=0.40).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD plus aspirin 75 to 162 mg QD vs aspirin 75 to 162 mg QD	CHARISMA trial) Patients 45 years of age or older with clinically evident cardiovascular disease or multiple atherothrombotic risk factors; patients receiving oral anticoagulation were excluded		cardiovascular causes Secondary: First occurrence of MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety	Secondary: There was no difference in the composite of stroke, MI, vascular death or rehospitalization (70 vs 66 patients; P=0.93) or all-cause mortality (29 vs 25 patients; P=0.69) among patients receiving clopidogrel plus aspirin and aspirin alone. Stroke (ischemic and hemorrhagic) occurred in 15 patients receiving clopidogrel plus aspirin (2.2% per year) and in 14 patients receiving aspirin alone (2.1% per year; HR, 1.03; 95% CI, 0.49 to 2.13; P=0.94). Severe or fatal extracranial hemorrhage occurred in 6 patients given clopidogrel plus aspirin vs 3 patients given aspirin alone (P=0.51), while intracranial bleeding occurred in 3 patients vs 1 patients (P=0.62), respectively.
Ho et al.[61] (2008) Clopidogrel (dose not specified)	RETRO Patients with ACS discharged on clopidogrel from Veterans Affairs hospitals	N=3,137 Duration varied	Primary: Rate of all-cause mortality or acute MI after stopping clopidogrel Secondary: Not reported	Primary: Among medically treated patients, mean duration of clopidogrel treatment was 302 days. Death or acute MI occurred in 17.1% of patients, with 60.8% of events occurring during 0 to 90 days, 21.3% during 91 to 180 days, and 9.7% during 181 to 270 days after stopping treatment with clopidogrel. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping treatment with clopidogrel was associated with a significantly higher risk of adverse events (IRR, 1.98; 95% CI, 1.46 to 2.69 vs the interval 91-180 days). Among the PCI-treated patients with ACS, mean duration of clopidogrel treatment was 278 days and death or acute MI occurred in 7.9% of patients, with 58.9% of events occurring during 0 to 90 days, 23.4% during 91 to 180 days, and 6.5% during 181 to 270 days after stopping clopidogrel treatment. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90-day interval after stopping clopidogrel treatment was associated with a significantly higher risk of adverse events (IRR, 1.82; 95% CI, 1.17 to 2.83).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Wiviott et al.[62] (2007) TRITON-TIMI 38 Clopidogrel 300 mg loading dose followed by 75mg daily plus aspirin 75 to 162 mg/daily vs prasugrel 60 mg loading dose followed by 10 mg daily plus aspirin 75 to 162 mg/daily	AC, DB, MC, RCT Patients with moderate-to-high risk ACS (unstable angina, NSTEMI, or STEMI) and scheduled PCI	N=13,608 Mean 14.5 months	Primary: Composite of death from CV causes, nonfatal MI, or nonfatal stroke Secondary: Stent thrombosis, composite of CV death, nonfatal MI, nonfatal stroke, or rehospitalization due to cardiac ischemic event, 30 and 90 day event rates for the primary endpoint and composite of CV death, nonfatal MI, or urgent target vessel revascularization	Primary: Compared to clopidogrel, treatment with prasugrel was associated with a reduction in the composite primary efficacy endpoint of death from CV causes, nonfatal MI, or nonfatal stroke (9.9 vs 12.1%, respectively; HR, 0.81; 95% CI, 0.73 to 0.9; P<0.001). This difference was driven primarily by a reduction in nonfatal MI, which was evident early on in therapy. Secondary: In a post-hoc analysis, probable or definite stent thrombosis was also significantly reduced in the prasugrel vs clopidogrel group (1.1 vs 2.4%; HR, 0.48; 95% CI 0.36 to 0.64; P<0.001), a finding that was observed with both bare metal and drug eluding stents. The composite of CV death, nonfatal MI, nonfatal stroke, and re-hospitalization for ischemia was 12.3% for prasugrel compared to 14.6% for clopidogrel (HR, 0.78; 95% CI, 0.69 to 0.89). The improvement in efficacy outcomes with prasugrel was accompanied by an increased risk of bleeding compared to clopidogrel. A higher percentage of patients treated with prasugrel had major bleeding than those treated with clopidogrel (2.4 vs 1.8%; P=0.03). There was a significant increase in life-threatening bleeding with prasugrel and a significant increase in fatal bleeding (0.4 vs 0.1%; P=0.002) compared to clopidogrel.
Wiviott et al.[63] (2008) Prasugrel 60 mg once, followed by 10 mg/day vs	Subanalysis of TRITON-TIMI 38 TRITON-TIMI 38 patients with a median age of 63 stratified by diabetes	N=13,608 (n=3,146 diabetes population) 6 to 15 months (median,	Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke	Primary: The composite endpoint in patients with diabetes was significantly lower in the prasugrel group (12.2%) than in the clopidogrel group (17.0%; HR, 0.70; 95% CI, 0.58 to 0.85; P<0.001). A 14.0% overall reduction in the primary endpoint was seen in the prasugrel and no diabetes group compared to the clopidogrel group (HR, 0.86; 95% CI, 0.76 to 0.98; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).		14.5 months)	Secondary: Rate of cardiovascular death, MI (fatal or nonfatal) or stent thrombosis; safety; net clinical benefit	Among the diabetes group the reduction was 30% in the prasugrel group compared to the clopidogrel group (HR, 0.70; 95% CI, 0.58 to 0.85; P<0.001). Secondary: The rate of cardiovascular death in patients with diabetes was not significantly lower in the prasugrel group (3.4%) than in the clopidogrel group (4.2%; HR, 0.85; 95% CI, 0.58 to 1.24; P=0.40). The rate of MI in patients with diabetes was significantly lower in the prasugrel group (8.2%) than in the clopidogrel group (13.2%; HR, 0.60; 95% CI, 0.48 to 0.76; P<0.001). The rate of MI in patients without diabetes was also significantly lower in the prasugrel group (8.7%) than in the clopidogrel group (7.2%; HR, 0.82; 95% CI, 0.72 to 0.95; P=0.006). There was an 18.0% reduction in MI among nondiabetic prasugrel patients compared to a 40.0% reduction in MI among diabetic prasugrel patients. The rate of stent thrombosis in patients with diabetes was significantly lower in the prasugrel group (2.0%) than in the clopidogrel group (3.6%; HR, 0.52; 95% CI, 0.33 to 0.84; P=0.007). The rate of TIMI major non-CABG bleeding in patients with diabetes was not significantly greater in the prasugrel group (2.5%) compared to the clopidogrel group (2.6%; HR, 1.06; 95% CI, 0.66 to 1.69; P=0.81). The rate of TIMI major or minor non-CABG bleeding in patients with diabetes was not significantly greater in the prasugrel group (5.3%) compared to the clopidogrel group (4.3%; HR, 1.30; 95% CI, 0.92 to 1.82; P=0.13). The rate of net clinical benefit was significantly greater in the prasugrel group (14.6%) than in the clopidogrel group (19.2%; HR, 0.74; 95% CI, 0.62 to 0.89; P=0.001).
Antman et al.[64] (2008)	Subanalysis of TRITON-TIMI 38	N=13,608 6 to 15	Primary: Rate of MI, stent thrombosis and	Primary: The rate of MI was significantly lower in the prasugrel group (4.27%) than in the clopidogrel group by day three (5.24%; HR, 0.81; 95% CI, 0.70 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	Patients with ACS (unstable angina, NSTEMI or STEMI) with a scheduled PCI; for patients with unstable angina or NSTEMI ischemic symptoms lasting ≥10 minutes and occurring within 72 hours of randomization, a TIMI score ≥3 and either ST-segment deviation ≥1 mm or elevated cardiac necrosis biomarker levels; STEMI patients were included within 12 hours after symptom onset if PCI was planned or within 14 days after receiving medical treatment for STEMI	months (median, 14.5 months)	urgent target vessel revascularization from randomization to day three and from day three to the end of the trial Secondary: Safety, percent net clinical benefit	0.95; P=0.008) and from day three until the end of the study (3.40 vs 4.79%; HR, 0.69; 95% CI, 0.58 to 0.83; P<0.0001). The rate of stent thrombosis was significantly lower in the prasugrel group than in the clopidogrel group by day three (0.33 vs 0.67%; HR, 0.49; 95% CI, 0.29 to 0.82; P=0.006) and from day three until the end of the study (0.08 vs 1.74%; HR, 0.45; 95% CI, 0.32 to 0.64; P<0.0001). The rate of urgent target vessel revascularization was significantly lower in the prasugrel group than in the clopidogrel group by day three (0.54 vs 0.83%; HR, 0.66; 95% CI, 0.43 to 0.99; P=0.047) and from day three until the end of the study (1.94 vs 2.97%; HR, 0.65; 95% CI, 0.52 to 0.82; P=0.0003). Secondary: Through the first three days the rate of TIMI major non-CABG bleeding was numerically greater in the prasugrel group (0.74%) compared to the clopidogrel group (0.61%), however the difference between the two groups was not significant, (P=0.35). From day three to the end of the trial prasugrel was associated with a significantly greater risk of TIMI major non-CABG bleeding (1.71%) compared to clopidogrel (1.23%; HR, 1.39; 95% CI, 1.02 to 1.89; P=0.036). The rate of net clinical benefit was significantly greater in the prasugrel group than in the clopidogrel group by day three (6.19 vs 5.29%; HR, 0.85; 95% CI, 0.74 to 0.98; P=0.025) and from day three until the end of the study (8.33 vs 7.35%; HR, 0.87; 95% CI, 0.77 to 0.98; P=0.028).
Murphy et al.[65] (2008) Prasugrel 60 mg once, followed by 10 mg/day vs	Subanalysis of TRITON-TIMI 38 Patients with ACS (unstable angina, NSTEMI or STEMI) with a scheduled PCI; for patients	N=13,608 6 to 15 months (median, 14.5 months)	Primary: Total number of reoccurrences of the composite endpoint (rate of death from cardiovascular causes, nonfatal	Primary: Prasugrel demonstrated a significant overall reduction in subsequent events with 195 fewer total primary events compared to clopidogrel (HR, 0.79; 95% CI, 0.71 to 0.87; P<0.001). From the time of the first event to the recurrent event or last follow up a second event occurred in 10.8% of the prasugrel group compared to 15.4% in the clopidogrel group (HR, 0.65; 95% CI, 0.46 to 0.92; P=0.016).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	with unstable angina or NSTEMI ischemic symptoms lasting ≥10 minutes and occurring within 72 hours of randomization, a TIMI score ≥3 and either ST-segment deviation ≥1 mm or elevated cardiac necrosis biomarker levels; STEMI patients were included within 12 hours after symptom onset if PCI was planned or within 14 days after receiving medical treatment for STEMI		MI or nonfatal stroke), risk of second event following initial event, cardiovascular deaths following nonfatal event Secondary: Safety	Cardiovascular death following the nonfatal event was also reduced in the prasugrel group (3.7%) compared to the clopidogrel group (7.1%; HR, 0.46; 95% CI, 0.25 to 0.82; P=0.008). Secondary: Recurrent bleeding events occurred infrequently, with TIMI major non-CABG bleeds in four patients treated with prasugrel and two with clopidogrel. There were also five repeat TIMI minor non-CABG bleeds in each treatment group. Among patients with at least one TIMI non-CABG major or minor bleeding event, 17 were reported in the prasugrel group and 13 were reported in the clopidogrel group.
Montalescot et al.[66] (2009) Clopidogrel 300 mg loading dose followed by 75mg daily plus aspirin 75 to 162 mg/daily vs prasugrel 60 mg loading dose followed by 10 mg daily plus aspirin 75 to 162 mg/daily	Subanalysis of TRITON-TIMI 38 Patients who presented within 12 hours of onset of symptoms of STEMI for whom primary PCI was planned	N=3,534 (Subgroup analysis of STEMI patients) 15 months	Primary: Composite of CV death, non-fatal MI, or non-fatal stroke Secondary: CV death, non-fatal MI, or urgent target vessel revascularization at 30 days	Primary: At 30 days, 115 (9.5%) individuals assigned prasugrel group had met the primary endpoint compared to 166 (9.5%) allocated to the clopidogrel group (HR, 0.68 [95% CI 0.54 to 0.87]; P=0.0017). This effect continued to 15 months (174 [10·0%] vs 216 [12·4%]; 0.79 [0.65 to 0.97]; P=0.0221). Secondary: At 30 days, the secondary endpoints of CV death, MI, or urgent target vessel revascularization were significantly reduced with prasugrel (HR, 0.75; 95% CI, 0.59 to 0.96; P=0.0205) and 15 months (HR, 0.79; 0.65 to 0.97; P=0.0250), as was stent thrombosis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Pride et al.[67] (2009) Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	Subanalysis of TRITON-TIMI 38 TRITON-TIMI 38 patients who underwent PCI without stent implantation	N=13,608 (n=569 PCI population) 6 to 15 months (median, 14.5 months)	Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke Secondary: Composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke or urgent target vessel revascularization; safety	Primary: The primary endpoint occurred in 14.2% of patients randomized to prasugrel and 17.1% of patients randomized to clopidogrel, a nonsignificant 18.0% RR reduction (HR, 0.82; 95% CI, 0.53 to 1.25; P=0.27). Overall, the unadjusted incidence of the primary composite outcome was significantly higher among patients who underwent PCI without stent implantation compared to those who received stents (15.6 vs 10.8%; P=0.001). Secondary: There were significant reductions in the incidence of urgent target vessel revascularization (3.6 vs 8.2%; HR, 0.46; 95% CI, 0.22 to 0.98; P=0.040), any target vessel revascularization (4.0 vs 10.1%; HR, 0.40; 95% CI, 0.20 to 0.82; P=0.009), the composite of any revascularization procedure (6.3 vs 12.9%; HR, 0.48; 95% CI, 0.27 to 0.87; P=0.014), and CABG surgery (12.5 vs 19.4%; HR, 0.62; 95% CI, 0.40 to 0.98; P=0.041) with prasugrel compared to clopidogrel. There were trends towards reductions in nonfatal MI (9.1 vs 13.5%; HR, 0.65; 95% CI, 0.39 to 1.10; P=0.11) and all MI (9.8 vs 13.9%; HR, 0.69; 95% CI, 0.41 to 1.14; P=0.14) favoring prasugrel. The incidence of all cause mortality, cardiovascular death and nonfatal and all stroke did not differ significantly between the groups. Non-CABG-related major bleeding was more frequent among patients randomized to prasugrel (2.1 vs 0.0%; P=0.033), and there was a trend toward an increased incidence of non-CABG-related life-threatening bleeding (1.7 vs 0.0%; P=0.057). The incidence of intracranial hemorrhage and the composite of non-CABG TIMI major and minor bleeding did not differ significantly between the groups (4.3 vs 2.2%; HR, 1.85; 95% CI, 0.63 to 5.42), although there was no significant interactions between bleeding rates and treatment with prasugrel compared to clopidogrel as a function of PCI stent (stent vs no stent).
O'Donoghue et al.[68] (2009)	Subanalysis of TRITON-TIMI 38	N=13,608 (n=7,414 GP	Primary: Composite of death	Primary: There was a consistent benefit of prasugrel over clopidogrel in reducing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	TRITON-TIMI 38 patients stratified by GB IIb/IIIa inhibitor use	IIb/IIIa inhibitor population) 30 days	from cardiovascular causes, nonfatal MI or nonfatal stroke Secondary: Periprocedural MI, urgent target vessel revascularization, stent thrombosis, safety	cardiovascular death, MI or stroke at 30 days in patients who did (HR, 0.76; 95% CI, 0.64 to 0.90) and did not (HR, 0.78; 95% CI, 0.63 to 0.97; P=0.83) receive a GP IIb/IIIa inhibitor. Secondary: Prasugrel significantly reduced the risk of recurrent MI in subjects by approximately 25% regardless of the use of a GP IIb/IIIa inhibitor, including a comparable benefit toward a reduction in periprocedural MI across both subgroups. Patients treated with prasugrel also exhibited a significant reduction in urgent target vessel revascularization, irrespective of whether or not they were treated with a GP IIb/IIIa inhibitor (P=0.63). At the end of 30 days, prasugrel significantly reduced the risk of stent thrombosis by 54% in patients treated with a GP IIb/IIIa inhibitor (HR, 0.46; 95% CI, 0.29 to 0.71) and by 66% in patients not treated with a GP IIb/IIIa inhibitor (HR, 0.34; 95% CI, 0.17 to 0.65; P=0.46). In the overall cohort, prasugrel significantly increased the risk of TIMI non-CABG-related major or minor bleeding compared to clopidogrel (2.6 vs 2.1; HR, 1.26; 95% CI, 1.01 to 1.57; P=0.04). The excess risk of TIMI non-CABG-related major or minor bleeding observed with prasugrel was comparable regardless of whether a GP IIb/IIIa inhibitor was used (HR, 1.16; 95% CI, 0.89 to 1.50) or was not used (HR, 1.63; 95% CI, 1.05 to 2.52; P=0.19). The absolute excess in the risk of TIMI non-CABG-related major bleeding with prasugrel vs clopidogrel was 0.1% in patients treated with a GP IIb/IIIa inhibitor (1.2 vs 1.1%; HR, 1.06; 95% CI, 0.69 to 1.64) and 0.3% in subjects not treated with a GP IIb/IIIa inhibitor (0.9 vs 0.6%; HR, 1.47; 95% CI, 0.81 to 2.66), a difference that was not significantly different between subgroups (P=0.39). Similarly, the relative hazard of TIMI life-threatening bleeding with prasugrel compared to clopidogrel did not differ significantly in the presence or absence of a GP IIb/IIIa inhibitor (P=0.19). The incidence of procedure-related TIMI major bleeding was similar for subjects treated with prasugrel or clopidogrel and was not significantly influenced by the use of a GP IIb/IIIa inhibitor (P value not reported). Consistent with the overall trial, there was no significant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				difference in the incidence of intracranial hemorrhage between treatment arms in either stratum (P value not reported).
Roe et al.[69] (2012) TRILOGY ACS Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who weighed <60 kg received 5 mg/day) vs clopidogrel 75 mg/day Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be	AC, DB, DD, event-driven, RCT Patients with ACS if selected for a final treatment strategy of medical management without revascularization within 10 days after the index event; patients with MI without ST-segment elevation had elevated cardiac markers and patients with unstable angina with negative cardiac markers had an ST-segment depression of >1 mm in ≥2 electrocardiographic leads, and patients had ≥1 of 4 risk criteria: age ≥60 years of age, the presence of diabetes, previous MI, or previous revascularization with either PCI or CABG	N=7,243 (primary analysis; patients <75 years of age) N=2,083 (secondary analysis; patients ≥75 years of age) Up to 30 months	Primary: Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke among patients <75 years of age Secondary: Incidence of cardiovascular death, MI, and stroke; all-cause mortality; bleeding events; safety	Primary: At a median follow-up of 17 months, the primary endpoint occurred in 13.9 vs 16.0% of prasugrel- and clopidogrel-treated patients (HR in the prasugrel group, 0.91; 95% CI, 0.79 to 1.05; P=0.21). Similar results were observed in the overall population (18.7 vs 20.3%; HR, 0.96; 95% CI, 0.86 to 1.07; P=0.45). Because superiority was not established in the primary cohort, the prespecified testing strategy did not direct further superiority testing. The frequency of the primary end point in the two treatment groups did not differ significantly among prespecified subgroups of patients who were <75 years of age, but an interaction with prasugrel treatment was apparent in current or recent smokers, those who underwent angiography before randomization, and those taking a PPI at randomization. The prespecified analysis that was performed to account for multiple recurrent ischemic events suggested a lower risk among patients <75 years of age with prasugrel (HR, 0.85; 95% CI, 0.72 to 1.00; P=0.04). Among patients who had an ischemic event, 364 patients treated with prasugrel (10.1%) had at least one ischemic event compared to 397 patients (11.0%) with clopidogrel, whereas 77 (2.1%) vs 109 (3.0%) had a least two recurrent ischemic events, and 18 (0.5%) vs 24 (0.7%) had at least three recurrent ischemic events, respectively. Secondary: Among patients <75 years of age, there were no differences in the incidences of cardiovascular death (6.6 vs 6.8%; HR, 0.93; 95% CI, 0.75 to 1.15; P=0.48), MI (8.3 vs 10.5%; HR, 0.89; 95% CI, 0.74 to 1.07; P=0.21), and stroke (1.5 vs 2.2%; HR, 0.67; 95% CI, 0.42 to 1.06; P=0.08) between prasugrel- and clopidogrel-treated patients. Similar results were observed in the overall population (P=0.38, P=0.58, and P=0.52) Among patients <75 years of age, all-cause mortality was similar between the two treatments (7.8 vs 8.1%; HR, 0.96; 95% CI, 0.79 to 1.16; P=0.63). Similar results were observed in the overall population (P=0.40).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treated with OL clopidogrel before randomization and were started on daily maintenance administration of a study drug after randomization.				At 30 months, the key bleeding end points of non-CABG-related severe or life-threatening events and major bleeding occurred with similar frequency among patients <75 years of age in the two treatment groups. The only subgroup in which there was a significant treatment interaction for TIMI major bleeding was patients receiving a reduced dose of aspirin. The frequency of new, benign neoplasms in the overall treated population did not differ significantly between prasugrel and clopidogrel (1.9 vs 1.8%; P=0.79); similar findings were observed among treated patients with no history of cancer or a history of previous cancer that had been cured before randomization. The incidence of common (>1.0%) nonhemorrhagic serious adverse events was balanced between the two treatments among patients <75 years of age, and the only significant difference observed was a higher rate of heart failure with clopidogrel.
Gurbel et al.[70] (2012) Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who weighed <60 kg received 5 mg/day) vs clopidogrel 75 mg/day Patients who underwent randomization within 72 hours after the first medical contact	Substudy of TRILOGY ACS Patients with ACS if selected for a final treatment strategy of medical management without revascularization within 10 days after the index event; patients with MI without ST-segment elevation had elevated cardiac markers and patients with unstable angina with negative cardiac markers had an ST-segment depression of >1 mm in ≥2	N=2,564 Up to 30 months	Primary: Platelet reactivity (measured in $P2Y_{12}$ reaction units); composite of cardiovascular death, MI, or stroke through 30 months Secondary: Not reported	Primary: Among patients <75 years of age and weighing ≥60 kg, median $P2Y_{12}$ reaction unit values at 30 days were 64 (interquartile range, 33-128) with prasugrel compared to 200 (interquartile range, 141-260) with clopidogrel (P<0.001), a difference that persisted through all subsequent time points. Among patients <75 years of age and weighing <60 kg, corresponding values were 139 (interquartile range, 86 to 203) vs 209 (interquartile range, 148 to 283) (P<0.001). Among patients >75 years of age, corresponding values were 164 (interquartile range, 105 to 216) vs 222 (interquartile range, 148 to 268) (P<0.001). At 30 months, the rate of the composite endpoint was 17.2 (160 events) vs 18.9% (180 events) with prasugrel and clopidogrel (P=0.29). There were no significant differences in the continuous distributions of 30 day $P2Y_{12}$ reaction unit values for patients with a primary efficacy endpoint compared to patients without an event (P=0.07) and no significant relationship between the occurrence of the primary efficacy endpoint and continuous $P2Y_{12}$ reaction unit values (adjusted HR for increase of 60 $P2Y_{12}$ reaction units, 1.03; 95% CI, 0.96 to 1.11; P=0.44). Similar findings were observed with 30 day $P2Y_{12}$ reaction unit cut points used to define high on-treatment platelet reactivity; $P2Y_{12}$ reaction unit >280 (adjusted HR, 1.16; 95% CI, 0.89 to 1.52; P=0.28) and $P2Y_{12}$ reaction unit >230

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be treated with OL clopidogrel before randomization and were started on daily maintenance administration of a study drug after randomization	electrocardiographic leads, and patients had ≥1 of 4 risk criteria: age ≥60 years of age, the presence of diabetes, previous MI, or previous revascularization with either PCI or CABG			(adjusted HR, 1.20; 95% CI, 0.90 to 1.61; P=0.21). Secondary: Not reported
Wallentin et al.[71] (2009) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received	AC, DB, DD, MC, PG, PRO, RCT Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation	N=18,624 12 months	Primary: Composite endpoint of the rate of vascular death, MI, or stroke; major bleeding Secondary: Effect in patients for whom invasive treatment was planned; composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of	Primary: At 12 months, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.92; P<0.001). A treatment effect was seen within 30 days and persisted throughout the trial. The rate of major bleeding was not different between ticagrelor and clopidogrel (11.6 vs 11.2%; HR, 1.04; 95% CI, 0.95 to 1.13; P=0.43). Secondary: In patients undergoing invasive procedures, significantly fewer composite events occurred with ticagrelor (8.9 vs 10.6%; HR, 8.4; 95% CI, 0.75 to 0.94; P=0.003). Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (10.2 vs 12.3%; HR, 0.84; 95% CI, 0.77 to 0.92; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.			vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; individual components of the primary endpoint; all-cause mortality; other bleeding events; dyspnea; bradyarrhythmia; any other adverse event; results of laboratory safety tests	Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other thrombotic event (14.6 vs 16.7; HR, 0.88; 95% CI, 0.81 to 0.95; P<0.001). The rates of MI (5.8 vs 6.9%; HR, 0.84; 95% CI, 0.75 to 0.95; P=0.005) and vascular death (4.0 vs 5.1%; HR, 0.84; 95% CI, 0.69 to 0.91; P=0.001) were significantly lower with ticagrelor. The rate of stroke was not different between the two treatments (1.5 vs 1.3%; HR, 1.17; 95% CI, 0.91 to 1.52; P=0.22). The rate of all-cause mortality was significantly lower with ticagrelor (4.5 vs 5.9%; HR, 0.78; 95% CI, 0.69 to 0.89; P<0.001). Data on minor bleeding events were not reported. Rates of fatal bleeding were not different between the two treatments (0.3 vs 0.3%; HR, 0.87; 95% CI, 0.48 to 1.59; P=0.66). The rate of fatal non-intracranial bleeding was significantly higher with clopidogrel (0.3 vs 0.1%, respectively; P=0.03). The rate of fatal intracranial bleeds was significantly higher with ticagrelor (0.10 vs 0.01%, respectively; P=0.02). The rate of dyspnea was significantly higher with ticagrelor (13.8 vs 7.8%; HR, 1.84; 95% CI, 1.68 to 2.02; P<0.001). From this group, 0.9 and 0.1% of patients discontinued treatment (HR, 6.12; 95% CI, 3.41 to 11.01; P<0.001). Rates of pacemaker insertion (P=0.87), syncope (P=0.08), bradycardia (P=0.21) and heart block (P=1.00) were not different between the two treatments. Laboratory testing revealed significant increases in baseline serum uric acid with ticagrelor at one (P<0.001) and 12 months (P<0.001). Similar results were observed with serum creatinine (P<0.001 for both). One month after the end of treatment, there were no differences between the two treatments for either serum uric acid (P=0.56) or creatinine (P=0.59).
James et al.	Substudy of PLATO	N=5,216	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011)[72] PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation, undergoing noninvasive procedures	12 months	Composite endpoint of the rate of vascular death, MI, or stroke; major bleeding events Secondary: Individual components of the primary composite endpoint; all-cause mortality; nonvascular mortality; composite of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; subclasses of stroke; other bleeding events	At 12 months, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (12.0 vs 14.3%; HR, 0.85; 95% CI, 0.73 to 1.00; P=0.045). The rate of major bleeding did not differ between ticagrelor and clopidogrel (11.9 vs 10.3%; HR, 1.17; 95% CI, 0.98 to 1.39; P=0.079). Secondary: The rate of vascular death was significantly lower with ticagrelor (5.5 vs 7.2%; HR, 0.76; 95% CI, 0.61 to 0.96; P=0.019). The rates of MI (7.2 vs 7.8%; HR, 0.94; 95% CI, 0.77 to 1.15; P=0.555) and stroke (2.1 vs 1.7%; HR, 1.35; 95% CI, 0.89 to 2.07; P=0.162) were not different between the two treatments. The rates of all-cause mortality was significantly lower with ticagrelor (6.1 to 8.2%; HR, 0.75; 95% CI, 0.61 to 0.93; P=0.010). The rate of nonvascular death was not different between the two treatments (0.6 vs 1.0%; HR, 0.68; 95% CI, 0.35 to 1.31; P=0.252). The rate of the composite of vascular death, MI, stroke, composite ischemic events, or other arterial thrombotic events was not different between the two treatments (18.6 vs 20.3%; HR, 0.94; 95% CI, 0.82 to 1.06; P=0.309). The rates of ischemic (1.5 vs 1.4%; P=0.530), hemorrhagic (0.5 vs 0.2%; P=0.069) or unknown (0.20 vs 0.06%; P=0.124) strokes were not different between the two treatments. The rates of life threatening or fatal (5.5 vs 5.6%; HR, 0.99; 95% CI, 0.77 to 1.26; P=0.911) and intracranial bleeding (0.5 vs 0.2%; HR, 2.83; 95% CI, 0.90 to 8.90; P=0.075) were not different between the two treatments. The rate of other major bleeding was significantly higher with ticagrelor (6.8 vs 4.9%; HR, 1.38; 95% CI, 1.09 to 1.76; P=0.009). The rates of non-CABG-related (P=1.03), CABG-related (P=0.335), coronary procedure related (P=0.231), noncoronary procedure related (P=0.072) bleeding were not different between the two treatments. The rate of major and minor

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				bleeding was significantly higher with ticagrelor (16.4 vs 14.4%; HR, 1.17; 95% CI, 1.01 to 1.36; P=0.0358).
Cannon et al.[73] (2010) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation, undergoing invasive procedures	N=13,408 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; total major bleeding Secondary: Composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; components of the primary endpoint; all-cause mortality; stent thrombosis; other bleeding events; safety	Primary: At 12 months, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (9.0 vs 10.7%; HR, 0.84; 95% CI, 0.75 to 0.94; P=0.0025). The rate of major bleeding did not differ between ticagrelor and clopidogrel (P=0.8803). Secondary: Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (9.4 vs 11.2%; HR, 0.84; 95% CI, 0.75 to 0.94; P=0.0016). Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, composite ischemic events or other arterial thrombotic events (9.4 vs 11.2%; HR, 0.85; 95% CI, 0.77 to 0.93; P=0.0005). The rates of MI (5.3 vs 6.6%; HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0023) and vascular death (3.4 vs 4.3%; HR, 0.82; 95% CI, 0.68 to 0.98; P=0.0250) were significantly lower with ticagrelor. The rate of stroke was not different between the two treatments (1.2 vs 1.1%; HR, 1.08; 95% CI, 0.78 to 1.50; P=0.6460). The rate of all-cause mortality was significantly lower with ticagrelor (3.9 vs 5.0%; HR, 0.81; 95% CI, 0.68 to 0.95; P=0.0054). The rates of definite (1.3 vs 2.0%; HR, 0.64; 95% CI, 0.46 to 0.88; P=0.0054), definite or probable (2.2 vs 3.0%; HR, 0.73; 95% CI, 0.57 to 0.94; P=0.0142) and total (definite, probable or possible) (2.8 vs 3.8%; HR, 0.73; 95% CI, 0.59 to 0.92; P=0.0068) stent thrombosis were significantly lower with ticagrelor. The rates of life-threatening or fatal (P=0.6095), intracranial (P=0.4364) and other major bleeding (P=0.4030) were not different between the two

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatments. The rates of total major or minor (P=0.0700), CABG-related (P=0.0710), coronary procedure-related (P=0.7768) and noncoronary procedure-related (P=0.3998) bleeding were not different between the two treatments. The rate of non-CABG-related bleeding was significantly higher with ticagrelor (8.9 vs 7.1%; HR, 1.26; 95% CI, 1.11 to 1.43; P=0.0004). The rate of dyspnea was significantly higher with ticagrelor (13.9 vs 8.0%; P<0.0001). Of the patients experiencing dyspnea, 0.8 and 0.2% discontinued treatment (P value not reported).
Steg et al.[74] (2010) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading	Substudy of the PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with ST-segment elevation or left bundle-branch block	N=7,544 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding Secondary: Composite endpoint of vascular death or MI (excluding silent); composite endpoint of all-cause mortality, MI (excluding silent), or stroke; composite endpoint of vascular death, total MI, stroke, severe recurrent cardiac ischemia, recurrent ischemia, TIA, or other arterial thrombotic events;	Primary: At 12 months, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (9.4 vs 10.8%; HR, 0.87; 95% CI, 0.75 to 1.01; P=0.07). The rate of major bleeding did not differ between ticagrelor and clopidogrel (HR, 0.98; 95% CI, 0.8 to 1.14; P=0.76). Secondary: Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death and MI (8.4 vs 10.2%; HR, 0.82; 95% CI, 0.71 to 0.69; P=0.01). Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (9.8 vs 11.3%; HR, 0.87; 95% CI, 0.75 to 1.00; P=0.05). Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, composite ischemic events or other arterial thrombotic events (13.3 vs 15.0%; HR, 0.87; 95% CI, 0.77 to 0.99; P=0.03). The rates of MI (4.7 vs 5.8%; HR, 0.80; 95% CI, 0.65 to 0.98; P=0.03) and stroke (1.7 vs 1.0%; HR, 1.63; 95% CI, 1.07 to 2.48; P=0.02) were significantly lower with ticagrelor, but not vascular death (4.5 vs 5.5%; HR, 0.83; 95% CI, 0.67 to 1.02; P=0.07).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose. In patients receiving a stent, 325 mg was allowed for 6 months.			components of the primary endpoint; all-cause mortality; severe recurrent cardiac ischemia; recurrent ischemia; TIA; arterial thrombotic events; stent thrombosis; safety	The rate of all-cause mortality was significantly lower with ticagrelor (5.0 vs 6.1%; HR, 0.82; 95% CI, 0.67 to 1.00; P=0.05). The rates of severe recurrent cardiac ischemia (2.7 vs 3.2%; HR, 0.81; 95% CI, 0.61 to 1.06; P=0.13), TIA (0.2 vs 0.2%; P value not reported) and arterial thrombotic events (0.3 vs 0.4%; HR, 0.65; 95% CI, 0.28 to 1.51; P=0.32) were not different between the two treatments. The rate of recurrent ischemia was significantly lower with ticagrelor (4.3 vs 5.1%; HR, 0.81; 95% CI, 0.65 to 1.01; P=0.05). The rates of definite or probable stent thrombosis was not different between the two treatments (2.6 vs 3.4%; HR, 0.74; 95% CI, 0.55 to 1.00; P=0.05). The rates of definite, probable or possible (3.3 vs 4.3%; HR, 0.75; 95% CI, 0.57 to 0.99; P=0.04) and definite (1.6 vs 2.4%; HR, 0.66; 95% CI, 0.45 to 0.95; P=0.03) stent thromboses were significantly lower with ticagrelor. The rates of fatal (P value not reported), life-threatening (P=0.86), major (P=0.76), major and minor (P=0.43), CABG-related (major; P=0.30, major and minor; P=0.26), non-CABG-related (major; P=0.61, major and minor; P=0.11), procedure-related (major; P=0.83, major and minor; P=0.72) and major non-procedure-related (P=0.30) bleeding were not different between the two treatments. The rate of non-procedure-related major and minor bleeding was significantly lower with clopidogrel (5.1 vs 3.7%; HR, 1.31; 95% CI, 1.04 to 1.66; P=0.02). The rate of dyspnea was significantly higher with ticagrelor (12.6 vs 8.4%; P<0.0001), and caused significantly more treatment discontinuations (0.5 vs 0.1%; P=0.0004). Rates of bradycardia (P=0.83), syncope (P=0.18), heart block (P=0.64) and pacemaker insertion (P=0.20) were not different between the two treatments.
James et al.[75] (2010) PLATO Ticagrelor 180 mg loading dose,	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous	N=15,202 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding	Primary: In patients with chronic kidney disease, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (17.3 vs 22.0%; HR, 0.77; 95% CI, 0.65 to 0.90; P=0.13). In patients with chronic kidney disease, there was no difference in the rate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	24 hours, with or without ST-segment elevation and chronic kidney disease (creatine clearance <60 mL/minute)		Secondary: All-cause mortality, other bleeding events, safety	of major bleeding between ticagrelor and clopidogrel (15.1 vs 14.3%; HR, 1.07; 95% CI, 0.88 to 1.03; P=0.92). Secondary: In patients with chronic kidney disease, the rate of all-cause mortality was not different between the two treatments (10.0 vs 14.0%; HR, 0.72; 95% CI, 0.58 to 0.89; P=0.16). In patients with chronic kidney disease, the rates of major or minor (P=0.54), non-CABG-related major (P=0.77), fatal major (P=0.06) and intracranial bleeding (P=0.69) were not different between the two treatments. In patients with chronic kidney disease, the rate of dyspnea was significantly less with clopidogrel (16.4 vs 11.5%; HR, 1.54; 95% CI, 1.27 to 1.88; P=0.04). In patients with chronic kidney disease, the rate of ventricular pauses was no different between the two treatments (5.4 vs 4.6%; HR, 1.16; 95% CI, 0.51 to 2.52; P=0.56).
James et al.[76] (2010) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation and	N=4,662 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding Secondary: All-cause	Primary: In patients with diabetes, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (14.1 vs 16.2%; HR, 0.88; 95% CI, 0.76 to 1.03). In patients with diabetes, there was no difference in the rate of major bleeding between ticagrelor and clopidogrel (14.1 vs 14.8%; HR, 0.95; 95% CI, 0.81 to 1.12).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	diabetes		mortality, MI, definite stent thrombosis, other bleeding events	Secondary: In patients with diabetes, the rate of all-cause mortality was not different between the two treatments (7.0 vs 8.7%; HR, 0.82; 95% CI, 0.66 to 1.01). In patients with diabetes, the rate of MI was not different between the two treatments (8.4 vs 9.1%; HR, 0.92; 95% CI, 0.75 to 1.13). In patients with diabetes, the rate of definite stent thrombosis was not different between the two treatments (1.6 vs 2.4%; HR, 0.65; 95% CI, 0.36 to 1.17). In patients with diabetes, the rates of non-CABG-related major (5.5 vs 4.9%; HR, 1.13; 95% CI, 0.86 to 1.49) and CABG-related major bleeding (9.3 vs 10.4%; HR, 0.90; 95% CI, 0.74 to 1.09) were not different between the two treatments.
Held et al.[77] (2011) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg	RETRO substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation who underwent CABG	N=1,261 12 months	Primary: Composite endpoint of vascular death, MI, or stroke after CABG; major CABG-related bleeding Secondary: Individual components of the	Primary: There was no difference between ticagrelor and clopidogrel with regards to the primary composite endpoint (10.6 vs 13.1%; HR, 0.84; 95% CI, 0.60 to 1.16; P=0.2862). There was no difference between ticagrelor and clopidogrel in the rate of major CABG-related bleeding (81.3 vs 80.1%; HR, 1.01; 95% CI, 0.90 to 1.15; P=0.84). Secondary: Rates of MI (excluding silent) (6.0 vs 5.7%; HR, 1.06; 95% CI, 0.66 to 1.68; P=0.8193) and stroke (2.1 vs 2.1%; HR, 1.17; 95% CI, 0.53 to 2.62;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.			primary endpoint after CABG; all-cause mortality after CABG; other bleeding events after CABG	P=0.6967) were not different between the two treatments. The rate of vascular death was significantly less with ticagrelor (4.1 vs 7.9%; HR, 0.52; 95% CI, 0.32 to 0.85; P=0.0092). The rate of all-cause mortality was significantly less with ticagrelor (4.7 vs 9.7%; HR, 0.49; 95% CI, 0.32 to 0.77; P=0.0018). The rates of life-threatening or fatal CABG-related bleeding were not different between the two treatments (42.6 vs 43.7%; HR, 1.02; 95% CI, 0.87 to 1.21; P=0.77).
Wallentin et al.[78] (2010) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD	Genetic (CYP 2C19 and ABCB1) substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation	N=10,285 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding (loss-of-function allele) Secondary: Composite endpoint of vascular death or MI, definite stent thrombosis, major bleeding (gain-of-	Primary: In patients with any loss-of-function allele, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (8.3 vs 10.7%; HR, 0.77; 95% CI, 0.60 to 0.99; P=0.0380). In patients with any loss-of-function allele, there was no difference in the rate of major bleeding between ticagrelor and clopidogrel (10.8 vs 10.4%; HR, 1.04; 95% CI, 0.82 to 1.30; P=0.77). Secondary: In patients with any loss-of-function allele, ticagrelor was association with significantly fewer events with regards to the composite of vascular death or MI (7.4 vs 9.9%; HR, 0.73; 95% CI, 0.51 to 0.95; P=0.0184). In patients with any loss-of-function allele, the rate of definite stent

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.			function allele), other bleeding events, net clinical benefit	thrombosis was not different between the two treatments (1.6 vs 2.2%; HR, 0.71; 95% CI, 0.36 to 1.37; P=0.30). In patients with any gain-of-function allele, the rate of major bleeding was not different between the two treatments (9.5 vs 10.8%; HR, 0.86; 95% CI, 0.71 to 1.05; P=0.13). In patients with any loss-of-function allele, the rates of non-CABG-related major (4.1 vs 3.0%; HR, 1.39; 95% CI, 0.93 to 2.08; P=0.11) and CABG-relate major bleeding (7.0 vs 7.8%; HR, 0.87; 95% CI, 0.66 to 1.14; P=0.31) were not different between the two treatments. In patients with any loss-of-function allele, the net clinical benefit was not different between the two treatments (14.7 vs 16.6%; HR, 0.88; 95% CI, 0.72 to 1.06; P=0.17). In patients with no loss-of-function, clopidogrel was significantly favored (13.4 vs 15.2%; HR, 0.86, 95% CI, 0.76 to 0.97; P=0.0172).
Mahaffey et al.[79] (2011) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation who received treatment in the United States	N=1,413 12 months	Primary: Composite endpoint of the vascular death, MI, or stroke; major bleeding Secondary: Individual components of the primary composite endpoint, all-cause mortality, other bleeding events	Primary: Within the United States, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 1.75; P=0.1459). For the rest of world, ticagrelor was significantly favored (9.0 vs 11.0%; HR, 0.81; 95% CI, 0.74 to 0.90; P<0.001). Within the United States, there was no difference in the rates of major bleeding between ticagrelor and clopidogrel (11.3 vs 11.0%; HR, 1.05; 95% CI, 0.76 to 1.45; P=0.7572). Secondary: Within the United States, the rates of vascular death (3.4 vs 2.7%; HR, 1.26; 95% CI, 0.69 to 2.31; P=0.4468), MI (9.1 vs 6.7%; HR, 1.38; 95% CI, 0.95 to 2.01; P=0.0956) and stroke (1.0 vs 0.6%; HR, 1.75; 95% CI, 0.51 to 0.597; P=0.3730) were not different between the two treatments. For the rest of world, ticagrelor was significantly favored for reducing vascular death (3.8 vs 4.9%; HR, 0.77; 95% CI, 0.67 to 0.89; P=0.0005)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.				and MI (5.1 vs 6.4%; HR, 0.80; 95% CI, 0.70 to 0.90; P=0.0004). Within the United States, the rate of all-cause mortality was not different between the two treatments (4.0 vs 3.4%; HR, 1.17; 95% CI, 0.68 to 2.01; P=0.5812). For the rest of world, ticagrelor was significantly favored (4.3 vs 5.6%; HR, 0.77; 95% CI, 0.67 to 0.88; P=0.0001). Within the United States, the rates of non-CAGB-related major (4.3 vs 3.7%; HR, 1.20; 95% CI, 0.70 to 2.04; P=0.5115) and major or minor bleeding (14.8 vs 13.6%; HR, 1.11; 95% CI, 0.84 to 1.84; P=0.4599) were not different between the two treatments. For the rest of the world, clopidogrel was significantly favored (3.9 vs 3.3%; HR, 1.19; 95% CI, 1.01 to 1.39; P=0.0330 and 14.5 vs 13.2%; HR, 1.11; 95% CI, 1.02 to 1.20; P=0.0114). For the entire population, results for the overall cohort yields an HR of 1.45 (95% CI, 1.01 to 2.09) favoring clopidogrel for maintenance aspirin doses ≥300 mg/day and HR of 0.77 (95% CI, 0.69 to 0.86) favoring ticagrelor for a maintenance aspirin dose ≤100 mg/day. The interaction between aspirin dose category and treatment is significant (P=0.00006). Within the United States, for patients receiving daily aspirin doses ≥300 mg, the event rate was 40 vs 27 with ticagrelor and clopidogrel (HR, 1.62; 95% CI, 0.99 to 2.94). The event rate was 19 vs 24 in patients receiving ≤100 mg/day of aspirin (HR, 0.73; 95% CI, 0.40 to 1.33).
Storey et al.[80] (2011) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose,	Substudy of PLATO Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation	N=199 12 months	Primary: FEV_1 after the completion of study treatment (six, nine, or 12 months depending on phase of entry into the PLATO trial) Secondary: FEV_1 after one month of treatment	Primary: FEV_1 values at the different evaluated time points were similar between treatments before and 20 minutes after inhalation of a β agonist (P values not reported). Secondary: There was no apparent change in FEV_1 before and 20 minutes after inhalation of a β agonist over time with either treatment and after the discontinuation of the study medication (P value not reported). Similar numbers of ticagrelor- and clopidogrel-treated patients showed >10% improvement in FEV_1 over time (seven and 12), with similar numbers of these patients showing improvement at the first visit after inhaled β agonist.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.			and one month after the discontinuation of treatment, other measures of pulmonary function, safety	The results of other pulmonary function parameters were also similar between the two treatments, with no apparent change over time and after discontinuation of study medication. Dyspnea or heart failure was noted in six and seven patients receiving ticagrelor and clopidogrel; pulmonary function parameters for these patients were consistent with findings in the rest of the treatment cohorts.
James et al.[81] (2012) PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD	Substudy of PLATO Adult patients with and without a history of prior stroke or TIA and who were hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation	N=18,624 12 months	Primary: Composite endpoint of the vascular death, MI or stroke and major bleeding Secondary: Components of primary composite endpoint and all-cause mortality	Primary: A total of 1,152 patients (6.2%) had a history of stroke or TIA. Overall, patients with prior history of stroke had higher rates of the primary composite endpoint compared to those without prior stroke or TIA; however, safety and efficacy in these patients were similar in the overall study population. The RR reduction of the primary composite endpoint with ticagrelor compared to clopidogrel was similar in patients with (HR, 0.87) and without (HR, 0.84) prior stroke or TIA (P=0.84). The risk of major bleeding with ticagrelor vs clopidogrel in patients with prior history of stroke or TIA was similar in patients without prior history (P=0.77). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.				When comparing patients with prior history of stroke or TIA to those without prior history, the RR reduction of cardiovascular death (P=0.42), MI (P=0.19) and overall stroke (P=0.89) was similar. The HR of all-cause mortality with ticagrelor compared to clopidogrel was 0.62 in patients with prior stroke or TIA and 0.81 in those without a prior history (P=0.19).
Procedures and/or Surgery				
Leon et al.[82] (1998) Aspirin 325 mg QD vs aspirin 325 mg QD and warfarin (dose adjusted to INR 2.0 to 2.5) vs aspirin 325 mg QD and ticlopidine 250 mg BID	MC, RCT Patients undergoing stent implantation	N=1,653 30 days	Primary: Composite of death, revascularization of target lesion, angiographically evident thrombosis or MI within 30 days Secondary: Achievement of <50% residual stenosis without death or emergency bypass surgery, procedure-related MI,	Primary: The primary end point was observed in 38 patients: 3.6% assigned to aspirin alone, 2.7% assigned to aspirin plus warfarin and 0.5% assigned to aspirin plus ticlopidine (P=0.001 for the comparison of all 3 groups). Secondary: Compared to aspirin alone, and aspirin plus warfarin, treatment with aspirin and ticlopidine resulted in a lower rate of stent thrombosis (P=0.001) following coronary stenting. Hemorrhagic complications occurred in 10 patients: 1.8% with aspirin alone, 6.2% with aspirin plus warfarin and 5.5% with aspirin plus ticlopidine (P<0.001 for the comparison of all 3 groups); the incidence of vascular surgical complications was 0.4, 2.0, and 2.0%, respectively (P=0.02). There were no significant differences in the incidence of neutropenia or thrombocytopenia among the 3 treatment groups and the overall incidence

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hematologic dyscrasias, hemorrhagic and vascular surgical complications	was 0.3%.
Ahn et al.[83] (2008) CIDES Aspirin 100 to 200 mg/day and cilostazol 200 mg/day vs aspirin 100 to 200 mg/day and clopidogrel 75 mg/day	MC, RCT Diabetic patients who underwent successful stenting	N=280 7.1 months (mean duration)	Primary: Change in luminal diameter Secondary: Rate of angiographic restenosis	Primary: The minimal luminal diameter at follow-up period for the aspirin and cilostazol group was 2.55 mm compared to 2.4 mm in the aspirin and clopidogrel group (P value not significant). Secondary: The rate of angiographic restenosis (stent plus 5-mm borders) was 9 (8.0%) in the aspirin and cilostazol group and 20 (16.1%) in the aspirin and clopidogrel group (P=0.041).
Lee et al.[84] (2008) DECLARE-DIABETES Aspirin 200 mg/day and clopidogrel 300 mg loading dose, followed by 75 mg QD vs aspirin 200 mg/day, clopidogrel 300 mg loading dose, followed by 75 mg	MC, PRO, RCT Diabetic patients ≥18 years of age undergoing drug-eluting stent implantation	N=400 9 months	Primary: In-stent late loss at six months Secondary: In-segment late loss and restenosis rate at six months; stent thrombosis, target vessel revascularization, major adverse cardiac events (death, MI, and target lesion revascularization) at 9 months; safety	Primary: At six months, the in-stent late loss was significantly lower in the triple therapy vs dual therapy group (0.25 vs 0.38 mm; P=0.025). Secondary: At six months, the in-segment late loss (0.42 vs 0.53 mm; P=0.031) and restenosis (8.0 vs 15.6%; P=0.033) were significantly lower in the triple therapy vs dual therapy group. At 9 months, there was no difference in the rate of stent thrombosis (0.0 vs 0.5%; P=0.999). Target vessel revascularization was lower in the triple therapy vs dual therapy group (3.5 vs 8.0%; P=0.053). At 9 months, major adverse cardiac events tended to be lower in the triple therapy than in the dual therapy group (3.0 vs 7.0%; P=0.066). Drug discontinuation was more common in the triple therapy vs dual

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD, and cilostazol 200 mg loading dose, followed by 100 mg BID				therapy group (14.5 vs 2.5%; P<0.001) with skin rash and gastrointestinal disturbance the most common reasons for termination of cilostazol.
Han et al.[85] (2009) Aspirin 300 mg QD for 1 month, followed by 100 mg QD and clopidogrel 300 ti 600 mg loading dose, followed by 75 mg QD vs aspirin 300 mg QD for 1 month, followed by 100 mg QD, clopidogrel 300 to 600 mg loading dose, followed by 75mg QD and cilostazol 100 mg BID	OL Patients aged 20 to 80 years admitted with ACS (unstable angina, NSTEMI, or STEMI) undergoing successful coronary stenting	N=1,212 12 months	Primary: Major adverse cardiac or cerebral event at one year (defined as the composite of cardiac death, nonfatal MI, stroke, or target vessel revascularization) Secondary: Bleeding events at one year	Primary: Triple-antiplatelet treatment was associated with a significantly lower incidence of the primary end points (10.3 vs 15.1%; P=0.011). The need for target vessel revascularization was similar between patients who received triple- and dual-antiplatelet treatment (7.9 vs 10.7%; P=0.10). Multivariate analysis showed that female patients and clinically or angiographically high-risk patients benefited more from the triple-antiplatelet treatment. Secondary: There were no significant differences between the two regimens in terms of the risks for major and minor bleeding.
Jeong et al.[86] (2009) ACCEL-RESISTANCE Aspirin 200 mg QD, clopidogrel 75 mg QD, and cilostazol 200 mg/day	RCT Patients with high post-treatment platelet reactivity undergoing coronary stenting	N=60 30 days	Primary: Platelet function Secondary: Not reported	Primary: After 30 days, significantly fewer patients in the triple vs high maintenance dose group had high post-treatment platelet reactivity (3.3 vs 26.7%; P=0.012). Percent inhibitions of 5 µmol/l ADP-induced Agg_{max} and late platelet aggregation (Agg_{late}) were significantly greater in the triple vs high maintenance group (51.1±22.5 vs 28.0±18.5%; P<0.001, and 70.9±27.3 vs 45.3±23.4%; P<0.001, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 200 mg QD and clopidogrel 150 mg QD				Percent inhibitions of 20 µmol/l ADP-induced Agg_{max} and $Aggl_{ate}$ were consistently greater in the triple vs high maintenance dose group. Percent change of P2Y12 reaction units demonstrated a higher antiplatelet effect in the triple vs high maintenance dose group (39.6±24.1 vs 23.1±29.9%; P=0.022). Secondary: Not reported
Mehta et al.[87] (2001) PCI-CURE Aspirin and clopidogrel or placebo prior to PCI; after PCI, stented patients received OL clopidogrel or ticlopidine in combination with aspirin for 2 two 4 weeks; then clopidogrel or placebo was resumed (for 3 two 12 months after initial randomization)	DB, RCT Patients with non-ST-elevation ACS from the CURE study undergoing PCI	N=2,658 Average duration of follow-up after PCI was 8 months	Primary: Composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days of PCI (main primary end point); cardiovascular death or MI from time of PCI to scheduled end of trial Secondary: Not reported	Primary: A total of 4.5% of patients in the clopidogrel and aspirin group reached the primary end point compared to 6.4% in the aspirin group (P=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI, or any revascularization (P=0.03) and of cardiovascular death or MI (P=0.047). Overall, clopidogrel was associated with a 31% reduction in cardiovascular death or MI, including events before and after PCI (P=0.002). At follow-up, there was no significant difference in major bleeding between the groups (P=0.64). Secondary: Not reported
Takeyasu et al.[88] (2005) Cilostazol 200 mg/day and aspirin 81 to 200 mg/day	OL, RCT Patients with ischemic heart disease receiving stents	N=642 6 months	Primary: Rate of stenosis according to qualitative coronary angiography analysis of	Primary: The rates of restenosis (27.8 vs 29.3%; P value not significant) and target lesion revascularization (22.4 vs 23.5%; P value not significant) were similar between patients receiving cilostazol and ticlopidine. The rate of subacute thrombosis was significantly greater with cilostazol than ticlopidine (2.5 vs 0.3%; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ticlopidine 200 mg/day and aspirin 81 to 200 mg/day			minimal lumen diameter of artery, safety Secondary: Not reported	There were no differences in the incidence of adverse reactions with the exception of purpura, which was reported more frequently with ticlopidine than cilostazol (1.0 vs 0.0%; P=0.045). Secondary: Not reported
Sabatine et al.[89] (2005) PCI-CLARITY Clopidogrel (300 mg loading dose, followed by 75 mg QD) plus aspirin (150 to 325 mg on the first day, followed by 75 to 162 mg QD) vs placebo plus aspirin (150 to 325 mg on the first day, followed by 75 to 162 mg QD)	DB, MC, PC, RCT Patients with STEMI who received fibrinolytics and underwent PCI (after mandated angiography in CLARITY-TIMI 28)	N=1,863 30 days	Primary: Composite of cardiovascular death, recurrent MI or stroke from PCI to 30 days after randomization Secondary: MI or stroke before PCI and the primary end point from randomization to 30 days	Primary: Pretreatment with clopidogrel in patients receiving concurrent aspirin significantly reduced the primary end point following PCI compared to aspirin alone (3.6 vs 6.2%; adjusted OR, 0.54; 95% CI, 0.35 to 0.85; P=0.008). Pretreatment with clopidogrel and aspirin also reduced the incidence of MI or stroke prior to PCI (4.0 vs 6.2%; OR, 0.62; 95% CI, 0.40 to 0.95; P=0.03). Secondary: Overall, pretreatment with clopidogrel significantly reduced the secondary outcome (7.5 vs 12.0%; adjusted OR, 0.59; 95% CI, 0.43 to 0.81; P=0.001). There was no significant excess in the rates of major or minor bleeding in patients receiving dual therapy vs aspirin alone (2.0 vs 1.9%, respectively; P>0.99).
Steinhubl et al.[90] (2002) CREDO Clopidogrel 300 mg loading dose (3 to 24 hours before PCI), then clopidogrel 75 mg QD through 12	DB, MC, PC, RCT Patients undergoing PCI	N=2,116 12 months	Primary: One-year incidence of the composite of death, MI, or stroke; 28-day incidence of the composite of death, MI or urgent target vessel revascularization	Primary: Long-term (one year) clopidogrel and aspirin therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke vs aspirin alone (95% CI, 3.9 to 44.4; P=0.02; absolute reduction, 3%). Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI or urgent revascularization at 28 days (-18.5%; 95% CI, -14.2 to 41.8; P=0.23). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months vs placebo (3 to 24 hours before PCI), then clopidogrel 75 mg QD through day 28, then placebo through 12 months All patients received aspirin 325 mg prior to PCI, then 325 mg QD through day 28, then 81m to 325 mg QD thereafter.			Secondary: Components of composite end points, administration of clopidogrel <6 hours or ≥6 hours before PCI, need for target vessel revascularization or any revascularization at one year	A similar level of benefit was found in the individual components of the primary end point at one year, although individual outcomes were not significant. Treatment randomization did not appear to influence the rate of target vessel revascularization or any other revascularization during the follow-up period. In a prespecified subgroup analysis, patients who had received clopidogrel at least 6 hours before PCI experienced a reduction in the relative combined risk of death, MI, or stroke by 38.6% (95% CI, -1.6 to 62.9; P=0.051) compared to no reduction when treatment was given less than 6 hours before PCI (P=0.051). Risk of major bleeding at one year increased, but not significantly (8.8% with clopidogrel vs 6.7% with aspirin alone; P=0.07).
Lev et al.[91] (2008) Clopidogrel 300 to 600 mg before PCI vs clopidogrel 300 to 600 mg immediately after PCI Patients were treated with aspirin before PCI, then aspirin and clopidogrel 75 mg QD for 3 to 12	PRO Patients with chest pain and STEMI undergoing emergency PCI	N=292 6 months	Primary: Occurrence of TIMI myocardial perfusion grade 3 after PCI Secondary: Incidence of reinfarction, stent thrombosis, target vessel revascularization, death	Primary: TIMI myocardial perfusion grade 3 occurred in a higher proportion of patients in the clopidogrel pretreatment group than in the no pretreatment group (85 vs 71%; P=0.01). Secondary: The incidence of reinfarction at 30 days (0.0 vs 3.2%, respectively; P=0.04) and six months (0.6 and 3.9%, respectively; P=0.09) was lower in the pretreatment group than in the no pretreatment group. The incidence of stent thrombosis at 30 days (0.0 vs 2.4%, respectively; P=0.08) and 6 months (0.0 and 3.9%, respectively; P=0.02) was lower in the pretreatment group than in the no pretreatment group. The incidence of death and target vessel revascularization were not significantly different between the two treatment groups at 30 days (P=0.6 and P=1.0) or six months (P=0.7 and P=0.9).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months after PCI				
Banerjee et al.[92] (2008) Clopidogrel for ≥1 year following PCI vs clopidogrel for <1 year following PCI Patients were free of cardiovascular events for 6 months after PCI, and had follow-up available for >12 months.	RETRO Patients who underwent PCI	N=530 2.4±0.8 years (mean follow-up)	Primary: All cause mortality Secondary: Incidence of major adverse cardiovascular events (composite of all cause death, nonfatal MI and repeat coronary revascularization by PCI or CABG)	Primary: Twelve (3.5%) patients who received clopidogrel for ≥1 year died compared to 28 (15%) patients who received clopidogrel for <1 year (P<0.001). On a multivariate analysis, the use of clopidogrel for ≥1 year was associated with lower mortality (HR, 0.28; 95% CI, 0.14 to 0.59; P<0.001), independent of traditional cardiovascular risk factors, clinical presentation and drug eluting stent use. Survival in the <1 and ≥1 year clopidogrel groups was 97 and 99%, respectively, at two years after PCI, and 80 and 93%, respectively, at three years after PCI. Secondary: There were no significant differences in the incidence of nonfatal MI (P=0.50), repeat coronary revascularization (P=0.16) or major adverse cardiovascular events between the two groups (P=0.10). Patients who experienced major adverse cardiovascular events were significantly older and had preexisting CAD, and those who died were more likely to have chronic renal disease and heart failure.
Han et al.[93] (2009) Clopidogrel 600 mg once, followed by 75 mg/day vs clopidogrel 600 mg once, followed by 150 mg/day All patients received aspirin 300 mg/day.	RCT Patients ≥18 years of age, diagnosed with ACS, planned pretreatment with 600 mg clopidogrel loading dose, presence of ≥1 severe coronary stenosis requiring PCI located in native arteries and suitable for drug eluting stent implantation	N=813 30 days	Primary: Major adverse cardiac event (composite of cardiac death, nonfatal MI and urgent target vessel revascularization) Secondary: Stent thrombosis, major and minor bleeding events	Primary: A total of 13 patients reached the primary end points, including four (1.0%) patients in the 150 mg group and nine (2.2%) patients in the 75 mg group (P>0.05). There was no significant difference in cumulative major adverse cardiac event-free survival between the two groups. The incidences of MI (two vs five; P>0.05), urgent target vessel revascularization (three vs eight; P>0.05) and cardiac death (one vs one; P>0.05) were similar between the two groups. Secondary: The incidence of stent thrombosis (zero vs six; P<0.05) was significantly lower in the 150 mg group compared to the 75 mg group. There was no significant differences between both groups regarding the risk of major (one vs zero; P>0.05) or minor (two vs one; P>0.05)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received dual antiplatelet therapy on admission followed by maintenance dose administration according to study protocol and PCI was performed within 48 hours of admission.				bleedings.
Valgimigli et al.[94] (2012) PRODIGY Clopidogrel 300 or 600 mg once, followed by 75 mg/day plus aspirin 160 to 325 mg orally or 500 mg intravenously once, followed by 80 to 160 mg/day for six months vs clopidogrel 300 or 600 mg once, followed by 75 mg/day plus aspirin 160 to 325 mg orally or 500 mg intravenously once,	MC, OL, RCT Patients ≥18 years of age with chronic stable CAD, NSTEMI or STEMI ACS who were receiving a stent placement	N=2,013 24 months	Primary: Composite of death of any cause, nonfatal MI and cerebrovascular accident Secondary: Components of the composite primary endpoint, cardiovascular death, stent thrombosis and bleeding outcomes	Primary: The cumulative risk of the primary endpoint at 24 months was 10.1% in the 24- month group and 10.0% in the six-month group (HR, 0.98; 95% CI, 0.74 to 1.29; P=0.91). Secondary: When individual components were analyzed separately, there were no differences between the six-month and 24-month groups with regard to risks of death of any cause (6.6% for both; HR, 1.00; 95% CI, 0.72 to 1.40; P=0.98), nonfatal MI (4.2 vs 4.0%; HR, 1.06; 95% CI, 0.69 to 1.63; P=0.80), cerebrovascular accident (1.4 vs 2.1%; HR, 0.60; 95% CI, 0.29 to 1.23; P=0.17), cardiovascular death (3.8 vs 3.7%; HR, 1.03; 95% CI, 0.66 to 1.61; P=0.89) and stent thrombosis (4.7 vs 3.9%; HR, 1.21; 95% CI, 0.79 to 1.86; P=0.38). Safety end point was a composite end point of fatal bleeding, overt bleeding plus hemoglobin drop of ≥3 g/dL, bleeding that requires nonsurgical/medical intervention, bleeding that leads to hospitalization or increased level of care and bleeding that prompts evaluation. Dual-antiplatelet therapy for six months was associated with a lower risk of bleeding compared to the 24-month therapy (3.5 vs 7.4%; HR, 0.46; 95% CI, 0.31 to 0.69; P=0.00018).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 80 to 160 mg/day for 24 months Patients in the six-month group who received bare metal stent were allowed to discontinue treatment after 30 days.				
Gwon et al.[95] (2012) EXCELLENT Clopidogrel 75 mg/day plus aspirin 100 to 200 mg/day for six months then aspirin alone for six months vs clopidogrel 75 mg/day plus aspirin 100 to 200 mg/day for 12 months All patients received aspirin ≥300 mg plus clopidogrel 300 to 600 mg once before PCI.	MC, OL, PRO, RCT Korean patients with coronary vessel occlusion and who were undergoing PCI with drug-eluting stent placement	N=1,443 12 months	Primary: Target vessel failure defined as a composite of cardiac death, MI and target vessel revascularization Secondary: Components of the composite primary endpoint, death of any cause, death or MI, stent thrombosis, major bleeding according to TIMI criteria, major adverse cardiocerebral events and composite safety endpoint	Primary: Incidence of target vessel failure was similar between the six- and 12-month dual antiplatelet treatment groups (4.8 vs 4.3%; HR, 1.14; 95% CI, 0.70 to 1.86). In the pre-specified subgroup analysis, the incidence of target vessel failure was higher with the six-month group compared to the 12-month group for patients with diabetes (HR, 3.16; 95% CI, 1.42 to 7.03). Secondary: No differences were seen between the six- and 12-month groups in the rate of cardiac death (0.3 vs 0.4%; HR, 0.67; 95% CI, 0.11 to 3.99), MI (1.8 vs 1.0%; HR, 1.86; 95% CI, 0.74 to 4.67) and target vessel revascularization (3.1 vs 3.2%; HR, 2.00; 95% CI, 0.75 to 5.34). Risk of death of any cause was 0.6 and 1.0% in the six-month and 12-month groups (HR, 0.57; 95% CI, 0.17 to 1.95). Death or MI occurred in 2.4 and 1.9% of patients in the six- and 12-month groups (HR, 1.21; 95% CI, 0.60 to 2.47). Incidence of stent thrombosis was higher with the six-month group but was not statistically different from the 12-month group (0.9 vs 0.1%; HR, 6.02; 95% CI, 0.72 to 49.96). Risk of TIMI major bleeding was similar between the six- and 12-month groups (0.3 vs 0.6%; HR, 0.5; 95% CI, 0.09 to 2.73).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Risk of major cardiocerebral event, which is a composite of death, MI, stroke, stent thrombosis and any revascularization, was similar between the six- and 12-month groups (8.0 vs 8.5%; HR, 0.94; 95% CI, 0.65 to 1.35). Safety endpoint, defined as a composite of death, MI, stroke, stent thrombosis and TIMI major bleeding, was also similar between the six- and 12-month groups (3.3 vs 3.0%; HR, 1.15; 95% CI, 0.64 to 2.06).
CURRENT-OASIS 7.[96] (2010) Clopidogrel 600 mg once, followed by 150 mg/day for 6 days, followed by clopidogrel 75 mg/day through day 30 (double dose) vs clopidogrel 300 mg once, followed by 75 mg/day for 6 days, followed by 75 mg/day through day 30 (standard dose) and aspirin ≥300 mg/day once, followed by 75 to 100 mg/day through	2x2 factorial design, RCT Patients ≥18 years of age who presented with a NSTE ACS or a STEMI	N=25,086 (n=17,263 underwent PCI) 30 days	Primary: Composite of cardiovascular death, MI or stroke Secondary: Composite of death from cardiovascular causes, MI, stroke or recurrent ischemia; the individual components of the primary endpoint; death from any cause; bleeding	Primary: The primary outcome occurred in 4.2% of patients in the double-dose group compared to 4.4% with the standard dose group (HR, 0.94; 95% CI, 0.83 to 1.06; P=0.30). Overall, 4.2% of the patients in the high-dose aspirin group had a primary outcome event compared to 4.4% of patients in the low-dose aspirin group (HR, 0.97; 95% CI, 0.86 to 1.09; P=0.61). A nominally significant interaction between the clopidogrel dose comparison and the aspirin dose comparison for the primary outcome was noted (P=0.04). Among patients assigned to high-dose aspirin, the primary outcome occurred in 3.8 and 4.6% in the double and standard clopidogrel dose groups (HR, 0.82; 95% CI, 0.69 to 0.98; P=0.03). Among patients assigned to low-dose aspirin, there was no significant difference between the double and standard clopidogrel groups (4.5 vs 4.2%; HR, 1.07; 95% CI, 0.90 to 1.26; P=0.46). Secondary: Consistent results were observed for each component of the primary outcome, as well as for the expanded composite endpoint for the clopidogrel and aspirin dose comparison. A nominally significant reduction in recurrent ischemia alone was associated with high-dose aspirin as compared to low-dose aspirin (0.3 vs 0.5%; HR, 0.63; 95% CI, 0.43 to 0.94; P=0.02). The rate of death from any cause did not differ significantly between the double and standard dose groups (2.3 vs 2.4%; HR with the double dose, 0.96; 95% CI, 0.82 to 1.13; P=0.61). Death from any cause occurred in 2.2

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
day 30 (low-dose) vs aspirin ≥300 mg/day once, followed by 300 to 325 mg/day through day 30 (high-dose) All patients were to undergo early angiography and PCI, if appropriate, no later than 72 hours after randomization.				and 2.5% of patients in the high- and low-dose groups (HR, 0.87; 95% CI, 0.74 to 1.03; P=0.10). Major bleeding occurred in 2.5 and 2.0% of patients in the double and standard dose groups (HR, 1.24; 95% CI, 1.05 to 1.46; P=0.01). The aspirin groups did not differ significantly with respect to major bleeding (P value not reported). There was a nominally significant increase in the increase of minor bleeding among patients who received high-dose aspirin (HR, 1.13; 95% CI, 1.00 to 1.27; P=0.04). There was a small increase in the incidence of major gastrointestinal bleeding among patients who received high-dose aspirin, as compared to those who received low-dose aspirin (0.4 vs 0.2%; P=0.04).
Bertrand et al.[97] (2000) CLASSICS Clopidogrel 300 mg loading dose, followed by 75 mg QD and aspirin 325 mg QD vs clopidogrel 75 mg QD and aspirin 325 mg QD vs ticlopidine 250 mg BID and aspirin 325	RCT Patients receiving a stent placement	N=1,020 28 days	Primary: Major peripheral or bleeding complications, neutropenia, thrombocytopenia or early discontinuation due to noncardiac adverse event Secondary: Incidence of cardiac events	Primary: Primary end point occurred in 4.6% of patients in the combined clopidogrel group and in 9.1% of patients in the ticlopidine group (RR, 0.50; 95% CI, 0.31 to 0.81; P=0.005). Secondary: Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups (1.2% with clopidogrel loading dose, 1.5% with clopidogrel without the loading dose and 0.9% with ticlopidine; P value not significant for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD				
Isshiki et al.[98] (2012) CLEAN Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 81 to 100 mg/day vs ticlopidine 100 mg BID plus aspirin 81 to 100 mg/day	DB, MC, RCT Japanese patients ≥20 years of with stable angina or history of MI and who were undergoing PCI	N=931 12 weeks	Primary: Composite of clinically significant bleeding, blood disorders, elevated liver function tests and study drug discontinuation due to an adverse reaction Secondary: Composite of all-cause mortality, acute MI, revascularization, stent thrombosis or ischemic stroke	Primary: The composite primary endpoint occurred in 10.1% of patients in the clopidogrel group and 34.2% in the ticlopidine group (HR, 0.259; 95% CI, 0.187 to 0.359; P<0.0001). When individual components were analyzed separately, there were no differences between clopidogrel and ticlopidine with regard to the risks of clinically significant bleeding (0.9 vs 0.6%; HR, 1.328; 95% CI, 0.297 to 5.936) and blood disorder (1.7 vs 3.4%; HR, 0.495; 95% CI, 0.212 to 1.158). Clopidogrel was associated with lower risk of liver function test elevation (6.0 vs 30.3%; HR, 0.172; 95% CI, 0.115 to 0.258) and treatment discontinuation due to an adverse reaction (3.9 vs 13.1%; HR, 0.281; 95% CI, 0.166 to 0.476) compared to ticlopidine. Secondary: There was no difference in the cumulative risk of the composite cardiovascular endpoint between the clopidogrel and ticlopidine groups (9.2 vs 10.3%; HR, 0.886; 95% CI, 0.587 to 1.337). Acute MI was reported in 7.7 and 9.2% of patients in the clopidogrel and ticlopidine groups, revascularization in 1.5 and 0.4% of patients and ischemic stroke in 0.2 and 0.6% of patients in the respective treatment group (P values not reported). No death or stent thrombosis was reported during the study.
Gao et al.[99] (2009) Clopidogrel 75 mg/day and aspirin 100 mg/day vs clopidogrel 75 mg/day	RCT Patients undergoing elective CABG	N=197 12 months	Primary: CABG graft patency rates Secondary: Not reported	Primary: At 1 month and 12 months after CABG graft patency rates of clopidogrel monotherapy group were, respectively, 99.0 and 96.9% for the left internal mammary artery, and 98.1 and 93.5% for the saphenous vein grafts. Those of the dual antiplatelet therapy group were, respectively, 98.9 and 97.8% for left internal mammary artery, and 98.2 and 96.3% for saphenous vein grafts. Thus, there were no significant differences in graft patency between the two groups (P>0.05). Secondary: Not reported
Park et al.[100] (2010)	OL	N=2,701	Primary: First occurrence of	Primary: The cumulative risk of the primary outcome at two years was 1.8% with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Clopidogrel 75 mg/day and aspirin (100 to 200 mg/day) vs aspirin 100 to 200 mg/day	Patients who had undergone drug eluting stent implantation ≥12 months prior to enrollment, who had not had a major cardiovascular event, or major bleeding since implantation	19.2 months (mean duration)	MI or death from cardiac causes after assignment to a treatment group Secondary: Death from any cause	dual antiplatelet therapy, as compared to 1.2% with aspirin monotherapy (HR, 1.65; 95% CI, 0.80 to 3.36; P=0.17). Secondary: There was no significant difference between the two treatment groups in the risk of individual secondary end points. In the dual antiplatelet therapy group as compared to the aspirin-monotherapy group, there was a nonsignificant increase in the composite risk of myocardial infarction, stroke, or death from any cause (HR, 1.73; 95% CI, 0.99 to 3.00; P=0.051) and in the composite risk of myocardial infarction, stroke, or death from cardiac causes (HR, 1.84; 95% CI, 0.99 to 3.45; P=0.06).
Sibbing et al.[101] (2009) Clopidogrel 75 mg/day vs pantoprazole vs omeprazole vs esomeprazole	CS, OB Patients on maintenance clopidogrel therapy scheduled for a coronary angiography who were also taking a PPI at the time point of platelet function testing	N=1,000 Duration varied	Primary: Platelet aggregation in patients treated with pantoprazole Secondary: Platelet aggregation in patients treated with omeprazole or esomeprazole	Primary: Those treated with pantoprazole (P=0.88) had similar platelet aggregation compared to those not treated with a PPI. Secondary: Those treated with omeprazole experienced significantly higher platelet aggregation compared to patients without PPI treatment (P=0.001). Those treated with esomeprazole (P=0.69) had similar platelet aggregation compared to those not treated with a PPI.
Trenk et al.[102] (2012) TRIGGER-PCI Prasugrel 60 mg loading dose followed by 10 mg/day	RCT Patients 18 to 80 years of age with stable CAD who underwent PCI with at least one drug-eluting stent placement and	N=423 6 months	Primary: Composite of cardiovascular death and MI and non-CABG-related TIMI major bleeding Secondary:	Primary: Composite primary endpoint occurred in one patient in the clopidogrel group vs none in the prasugrel group (P>0.05). Non-CABG-related TIMI major bleeding occurred in three patients in the prasugrel group and one in the clopidogrel group (P>0.05). Secondary: Composite endpoint of cardiovascular death, MI and revascularization

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clopidogrel 75 mg/day All patients received clopidogrel 600 mg loading dose plus aspirin ≥250 mg within 24 hours before PCI and one-time clopidogrel 75 mg the morning after PCI.	demonstrated high on-treatment platelet reactivity after clopidogrel loading dose followed by one-time clopidogrel 75 mg		Composite of cardiovascular death, MI and target vessel revascularization, composite of cardiovascular death, MI, stroke and rehospitalization for cardiac ischemic event and composite safety endpoint	occurred in two patients in each treatment group (P>0.05). Composite endpoint of cardiovascular death, MI, stroke and rehospitalization for cardiac ischemic event occurred in two patients treated with prasugrel and six patients treatment with clopidogrel (HR, 0.493; 95% CI, 0.090 to 2.692). Secondary safety endpoint, a composite of any non-CABG-related bleeding, occurred in 2.9 and 1.9% in the prasugrel and clopidogrel groups, respectively (HR, 1.517; 95% CI, 0.428 to 5.376). The authors concluded that due to low event rate, the utility of prasugrel in patients with high on-treatment platelet reactivity could not be determined.
Wiviott et al.[12] (2007) Prasugrel 60 mg loading dose, followed by 10 mg/day vs clopidogrel 600 mg loading dose, followed by 150 mg/day Maintenance dose administered upon PCI completion.	AC, DB, DD, RCT, XO Patients ≥18 years of age, who were scheduled to undergo cardiac catheterization with planned PCI for angina and ≥1 of the following: angiograph within 14 days with ≥1 PCI amendable legion, objective findings of ischemia within 8 weeks of study, or prior PCI or CABG	N=201 28 days (treatment periods were 14 days each)	Primary: Inhibition of platelet aggregation with 20 µmol/L adenosine diphosphate at six hours during the loading dose phase and at 14±2 days of the maintenance dose Secondary: Mean maximal platelet aggregation with 20 µmol/L adenosine diphosphate, mean $P2Y_{12}$ assay percent inhibition,	Primary: For the loading dose phase, mean inhibition of platelet aggregation with 20 µmol/L adenosine diphosphate at six hours was significantly greater (higher inhibition of platelet aggregation indication of greater antiplatelet effect) in the prasugrel group (74.8%) compared to the clopidogrel group (31.8%). The mean difference between the two groups was 43.2% (P<0.0001). For the maintenance dose phase mean inhibition of platelet aggregation with 20 µmol/L adenosine diphosphate at 14±2 days was significantly greater in the prasugrel group (61.3%) compared to the clopidogrel group (46.1%). The mean difference between the two groups was 14.9% (P<0.0001). Secondary: For the loading dose phase mean maximal platelet aggregation with 20 µmol/L adenosine diphosphate was significantly lower (lower maximal platelet aggregation indication of greater antiplatelet effect) in the prasugrel group (18.9%) compared to the clopidogrel group (52.1%). The mean difference between the two groups was 33.1% (P<0.0001). For the maintenance dose phase mean maximal platelet aggregation with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			safety	20 μmol/L adenosine diphosphate at 14±2 days was significantly lower in the prasugrel group (29.2%) compared to the clopidogrel group (40.9%). The mean difference between the two groups was 11.3% (P<0.0001). For the loading dose phase prasugrel also showed significantly greater platelet inhibition with the $P2Y_{12}$ assay (89.5%) compared to clopidogrel (38.4%). The mean difference between the two groups was 51.4% (P<0.0001). For the maintenance dose phase prasugrel also showed significantly greater platelet inhibition with the $P2Y_{12}$ assay (83.3%) compared to clopidogrel (65.1%). The mean difference between the two groups was 18.9% (P<0.0001). There were no TIMI major bleeding episodes in either treatment group. For TIMI minor bleeding episodes 2% of patients in the prasugrel group experienced a minor bleed compared to 0% in the clopidogrel group. In the prasugrel group 18.6% of the patients reported a hemorrhagic event whether minor or major, compared to 14.1% in the clopidogrel group, however the difference was not significant (P value not reported).
Peripheral Artery Disease				
Berger et al.[103] (2009) Aspirin vs aspirin/ dipyridamole vs placebo	MA (18 trials) Patients with PAD	N=5,269 Duration varied	Primary: Relative risk reduction of aspirin therapy on the composite end point of nonfatal MI, nonfatal stroke, and cardiovascular death Secondary: All-cause mortality and each component of the	Primary: There was no overall statistically significant difference in the composite outcome of nonfatal MI, nonfatal stroke and cardiovascular death between the aspirin and placebo or control groups (18 RCTs: RR, 0.88; 95% CI, 0.76 to 1.04) There was a significantly lower incidence of nonfatal stroke in the aspirin groups (18 RCTs: RR, 0.66; 95% CI, 0.47 to 0.94). Secondary: There were no statistically significant differences between the groups for any other secondary efficacy outcome. There was no statistically significant difference between the groups in incidence of major bleeding, but this was not formally assessed in many

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			primary end point	included RCTs.
Hiatt et al.[104] (2008) CASTLE Cilostazol 50 to 100 mg BID vs placebo	DB, MC, PA, PC, RCT Patients ≥17 years with a clinical diagnosis of PAD and symptoms of claudication	N=1,435 Up to 3.5 years	Primary: All-cause mortality on treatment (defined as period while taking the study drug and for 30 days after discontinuing therapy) Secondary: Safety	Primary: Long-term adherence to cilostazol was poor with >60% of participants discontinuing therapy by 36 months. There were 18 deaths in patients receiving cilostazol (N=717) and 19 deaths in patients receiving placebo (N=718) (HR, 0.99; 95% CI, 0.52 to 1.88). The study was underpowered to meet its primary end point. In the full ITT population at 36 months, there were 49 deaths for cilostazol patients and 52 deaths for placebo patients (HR, 0.94; 95% CI, 0.64 to 1.39). Thus most deaths occurred >30 days after study drug discontinuation. The incidence of cardiovascular deaths was similar between the two treatment groups (14 patients in each group). Secondary: Serious bleeding events affected 18 patients taking cilostazol and 22 patients taking placebo. The rates of bleeding events were similar in patients who used aspirin, aspirin plus clopidogrel or anticoagulants at anytime during the course of the study.

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice-daily, ER=extended-release, IR=immediate-release, QD=once-daily
Study abbreviations: AC=active-controlled, CS=cross sectional, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OB=observational, OL=open-label, PA=parallel arm, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=cross over trial
Miscellaneous abbreviations: ACS=acute coronary syndrome, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, CT=computerized tomography, CV=cardiovascular, FEV_1=forced expiratory volume in one second, GFR=glomerular filtration rate, GP IIb/IIIa inhibitor=glycoprotein IIb/IIIa inhibitor, HR=hazard ratio, INR=International Normalized Ratio, IRR=incidence rate ratio, ITT=intention to treat, IU=international units, MES=microembolic signal, MI=myocardial infarction, MRI=magnetic resonance imaging, NSTE ACS=non-ST-segment elevation acute coronary syndromes, NSTEMI=non-ST-segment elevation myocardial infarction, OR=odds ratio, PAD=peripheral arterial disease, PCI=percutaneous coronary intervention, PPI=proton pump inhibitor, RR=relative risk, STEMI=ST-segment elevation myocardial infarction, TIA=transient ischemic attack, TIMI=thrombolysis in myocardial infarction

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 14. Relative Cost of the Platelet-Aggregation Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Aspirin	chewable tablet, delayed-release tablet, packet, rectal suppository, tablet	Ecotrin®*‡, Stanback Analgesic®‡	$	$
Cilostazol	tablet	Pletal®*	$$$$	$
Clopidogrel	tablet	Plavix®*	$$$$	$
Dipyridamole	injection, tablet	Persantine®*	$$$$	$
Prasugrel	tablet	Effient®	$$$$	N/A
Ticagrelor	tablet	Brilinta®	$$$$$	N/A
Ticlopidine	tablet	N/A	N/A	$$
Combination Products				
Aspirin and dipyridamole	extended-release capsule	Aggrenox®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
‡Product is available over-the-counter.
N/A=Not available.

X. Conclusions

The platelet-aggregation inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. They are approved for the treatment and/or prevention of acute coronary syndromes (ACS), angina, intermittent claudication, myocardial infarction (MI), stroke, and transient ischemic attack (TIA). They are also approved for the prevention of thrombosis in patients undergoing cardiovascular procedures and/or surgery.[1-9] Cilostazol, clopidogrel, dipyridamole, and ticlopidine are available in a generic formulation. Aspirin is also available over-the-counter. The fixed-dose combination of aspirin and dipyridamole (Aggrenox®) is not interchangeable with the generic formulations of aspirin and dipyridamole since the strengths and delivery mechanisms are different among these products.[1-3]

Aspirin has been the most frequently studied platelet-aggregation inhibitor and is usually the reference drug to which other treatments are compared.[49] Aspirin is the platelet-aggregation inhibitor recommended as first-line in most treatment guidelines for general use. Aspirin is recommended as a first-line option for the initial management of noncardioembolic stroke or TIA, ACS, and MI, as well as for primary and secondary prevention in patients with cerebrovascular, cardiovascular, and peripheral vascular diseases. Low-dose aspirin (75 to 150 mg/day) is an effective platelet-aggregation inhibitor regimen for long-term use, but in acute settings, an initial loading dose of ≥150 mg may be required. Other platelet inhibitors are usually reserved for patients with contraindications or severe intolerance to aspirin or who have failed aspirin monotherapy or in high-risk patients when dual antiplatelet therapy is recommended. Dual antiplatelet therapy with aspirin plus clopidogrel, prasugrel, or ticagrelor is recommended for patients with ACS (non ST-segment elevation myocardial infarction [NSTEMI] and unstable angina). Antiplatelet therapy is also recommended in patients with ST-segment elevation myocardial infarction (STEMI). For patients with noncardioembolic ischemic strokes or TIAs, fixed-dose aspirin and dipyridamole is suggested instead of aspirin alone, and clopidogrel may be considered instead of aspirin alone to reduce the risk of recurrent stroke and other cardiovascular events.[10,16,17,18,20,23,24] In a trial comparing aspirin plus dipyridamole extended-release and clopidogrel (with or without telmisartan), results demonstrated that neither treatment was more effective compared to the other in the prevention of recurrent stroke.[39] For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination product has been studied in patients who have had an event while receiving aspirin.[16]

Clopidogrel and ticlopidine are adenosine diphosphate receptor antagonists and have been shown to significantly reduce the odds of a serious vascular event in high-risk patients. The CAPRIE trial reported that clopidogrel significantly reduced the combined risk of ischemic stroke, MI, and vascular death by 8.7% compared to aspirin in patients with a recent ischemic stroke, MI, or established peripheral vascular disease. In a subanalysis of over 6,000 patients who were enrolled in the trial based on a recent ischemic stroke, clopidogrel reduced the risk of the composite endpoint by 7.3% and stroke by 8.0% compared to aspirin; however, these differences were not statistically significant.[51] On the basis of the CURE, COMMIT, and CLARITY trials, clopidogrel received a Food and Drug Administration (FDA) indication for the reduction of atherothrombotic events in patients with ACS and MI, and clopidogrel has been incorporated into the current treatment guidelines for the management of these conditions.[17,20,54,55,89] Prasugrel is a relatively new adenosine diphosphate receptor antagonist which has been reported to be the most potent of these agents and to have more desirable characteristics when compared to clopidogrel with regards to drug-drug interactions and interpatient enzyme variability.[11-13] Approval of this agent was based on the results from the TRITON-TIMI 38 trial, in which prasugrel was significantly more effective in reducing ischemic events in patients with ACS who underwent percutaneous coronary intervention (PCI) intervention. Of note, no reduction in the mortality rate was seen with prasugrel, and a significantly greater incidence of major, minor, life-threatening, and fatal bleeding events was associated with prasugrel.[82] A focused update from the American College of Cardiology/American Heart Association recommends the use of prasugrel in patients with a STEMI in which PCI is planned. The overall recommendation is for a thienopyridine to be used in these patients, with both clopidogrel and prasugrel listed as potential options. Of note, use of prasugrel in STEMI patients with a prior history of stroke or TIA for whom primary PCI is not recommended.[20]

Ticagrelor is the newest platelet inhibitor to be FDA-approved, specifically to reduce the rate of thrombotic cardiovascular events in patients with ACS, including unstable angina, NSTEMI, and STEMI.[5] As a cyclopentyltriazolopyrimidine, ticagrelor works in a similar manner to the other thienopyridine platelet inhibitors (clopidogrel, prasugrel, ticlopidine); however, ticagrelor is a reversible inhibitor of the $P2Y_{12}$ receptors. In addition, ticagrelor is not a prodrug and therefore does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.[2,5] The pivotal clinical trial establishing the safety and efficacy of ticagrelor in reducing the rate of thrombotic cardiovascular events in patients with ACS is the PLATO trial. PLATO was a large, international, prospective, double-blind, randomized-controlled trial comparing ticagrelor and clopidogrel in hospitalized patients with documented ACS, with or without ST-segment elevation (N=18,624). After 12 months of treatment, ticagrelor significantly reduced the primary composite endpoint of cardiovascular death, MI, or stroke, without increasing the risk of major bleeding.[54] Within the United States, clopidogrel, prasugrel, and ticagrelor are all recommended as potential options in patients receiving PCI, while clopidogrel and ticagrelor are both recommended as potential options in patients with unstable angina/NSTEMI who are not undergoing PCI.[17,23] The 2011 European Society of Cardiology guidelines recommend that patients presenting without persistent ST-elevation receive dual antiplatelet therapy with aspirin and a platelet inhibitor. Specifically, ticagrelor is recommended for all patients at moderate to high risk of ischemic events, regardless of initial treatment strategy (i.e., invasive vs noninvasive), including those pretreated with clopidogrel. Prasugrel is recommended for $P2Y_{12}$ inhibitor-naïve patients who are proceeding to PCI, while clopidogrel is recommended for patients who cannot receive ticagrelor or prasugrel.[18]

Clinical trials have shown that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. Randomized trials that compared ticlopidine with aspirin in stroke or TIA patients produced conflicting results regarding whether ticlopidine is more effective than aspirin.[46,47] When compared to aspirin alone, and aspirin plus warfarin, treatment with aspirin plus ticlopidine resulted in a lower rate of stent thrombosis following coronary stenting.[82] Because ticlopidine is associated with a risk of life-threatening blood dyscrasias, ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.[1,2]

Dipyridamole has been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease compared to placebo, but has not been shown to be more effective than aspirin.[32,33] Aspirin plus dipyridamole significantly reduced the risk of stroke by 37% compared to 18% with aspirin and 16% with dipyridamole. There was no significant difference in all cause mortality among the active treatment groups.[32] Aspirin plus dipyridamole significantly reduced the composite of death, nonfatal stroke or MI and major bleeding to 13% of patients compared to 16% for aspirin monotherapy; however, the combination regimen was discontinued more often, mainly because of headache.[35]

The effectiveness of clopidogrel is dependent on its activation to an active metabolite by cytochrome p450 (CYP) 2C19. Clopidogrel forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Consider alternative treatments in patients identified as CYP2C19 poor metabolizers.[8] Prasugrel can cause significant bleeding and should not be used in patients with active bleeding or a history of TIA or stroke. It is also not recommended in patients ≥75 years of age due to the increased risk of fatal and intracranial bleeding and because of uncertain benefit, except in high-risk situations.[6] Because ticlopidine is associated with a risk of life-threatening blood dyscrasias, it should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.[1,2]

Therefore, all brand platelet-aggregation inhibitors within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. The fixed-dose combination of aspirin and extended-release dipyridamole (Aggrenox®) should be available as first-line therapy through the medical justification portion of the prior authorization process for patients who have experienced an ischemic stroke or TIA. Prasugrel (Effient®) and ticagrelor (Brilinta®) should be available as first-line therapy (in combination with aspirin) through the medical justification portion of the prior authorization process for patients who have experienced an ACS who are going to be managed medically or with PCI.

XI. Recommendations

No brand platelet-aggregation inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antiarrhythmic Agents
AHFS Class 240404
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I. Overview

Cardiac contractions are regulated by electrical activity in the heart originating in the sinoatrial node and propagated through ion channels, chiefly sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-) channels. Arrhythmias are caused by abnormalities in formation and transmission of impulses and are classified based on their origin: supraventricular (atrial or atrioventricular junction) or ventricular.[1]

Research in recent years has provided extensive data regarding the cellular mechanisms by which some of the antiarrhythmic drugs exert their action; however, the general approach to antiarrhythmic therapy remains largely empirical.[2] The antiarrhythmic agents are generally grouped into specific categories or classes based on their predominant mechanisms: (1) sodium channel blockade, (2) blockade of sympathetic autonomic effects in the heart, (3) prolongation of the effective refractory period, and (4) calcium channel blockade.[1] E. M. Vaughan Williams proposed the first antiarrhythmic classification system in 1970 and it is now the most widely used scheme. The Vaughan Williams classification system divides the antiarrhythmic agents into the following classes: Class I: fast sodium channel blockers, Class II: β-blockers, Class III: repolarization potassium current blockers, Class IV: calcium channel antagonists.[2] The agents included in this review differ with regards to their Food and Drug Administration-approved indications, mechanism of action, pharmacokinetic properties, drug interactions, and adverse events.

The antiarrhythmic agents that are included in this review, as well as their Vaughan Williams Classifications, are listed in Table 1. This review encompasses all dosage forms and strengths. All of the antiarrhythmic agents are available in a generic formulation, with the exception of dofetilide and dronedarone. This class was last reviewed in August 2010.

Table 1. Antiarrhythmic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Vaughan Williams Classification	Current PDL Agent(s)
Amiodarone	injection, tablet	Cordarone®*, Nexterone®, Pacerone®*	III	amiodarone
Disopyramide	capsule, extended-release capsule	Norpace®*, Norpace CR®	IA	disopyramide
Dofetilide	capsule	Tikosyn®	III	none
Dronedarone	tablet	Multaq®	I, II, III, IV	none
Flecainide	tablet	Tambocor®*	IC	flecainide
Mexiletine	capsule	N/A	IB	mexiletine
Propafenone	extended-release capsule, tablet	Rythmol®*, Rythmol SR®*	IC	propafenone
Quinidine	extended-release tablet, injection, tablet	N/A	IA	quinidine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.
N/A=Not available.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the antiarrhythmic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antiarrhythmic Agents

Clinical Guideline	Recommendation (s)
North American Society of Pacing and Electrophysiology/Heart Rhythm Society Practice Guidelines Subcommittee: **A Practical Guide for Clinicians Who Treat Patients With Amiodarone[3] (2007)**	Ventricular arrhythmias • Oral amiodarone is the recommended agent of choice for use in combination with additional appropriate therapies, including β-blockers, in patients with sustained ventricular tachyarrhythmias associated with structural heart disease, especially those with left ventricular dysfunction, and who are not candidates for an implantable cardioverter-defibrillator. • It is recommended that amiodarone therapy be reserved for symptomatic patients with non-sustained ventricular tachyarrhythmias that are refractory to β-blocker therapy and concerning enough to require treatment. Atrial fibrillation (AF) • This guideline refers to the recommendations provided by the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines that recommend oral amiodarone be used for treatment of AF in particular subsets of patients including: 1) patients post-myocardial infarction (MI) who are not candidates for sotalol or dofetilide; 2) those with congestive heart failure (CHF)and left ventricular dysfunction who are not candidates for dofetilide; 3) patients with significant left ventricular hypertrophy, and 4) those symptomatic patients who are refractory to antiarrhythmic treatments and an alternative to catheter ablation is preferred. • Amiodarone therapy should only be considered in those patients with AF who need ventricular rate control and have failed or are unable to use other appropriate agents including digoxin, β-blockers, or calcium channel blockers. • If prophylactic amiodarone therapy is to be used prior to aortocoronary bypass surgery, it is recommended to only consider this therapy in those patients that are high-risk (prior history of AF, valve replacement surgery) and therapy with β-blocker monotherapy will most likely still be associated with a high post-operative AF occurrence rate. Pregnant patients • Due to some unfavorable characteristics possessed by amiodarone, including end-organ toxicity, therapy with it in pregnant patients is not recommended unless there are no other treatment options available. Pediatric patients • There is a lack of data studying intravenous amiodarone in pediatric patients; however, in some lethal tachyarrhythmias, amiodarone is often used in these situations. • It is recommended that children receiving amiodarone therapy be supervised by a pediatric electrophysiologist. Patient follow-up • Patient follow-up is recommended for patients receiving amiodarone therapy for either atrial or ventricular arrhythmias. • Follow-up recommendations include continued assessment of drug

Clinical Guideline	Recommendation (s)
	therapy, efficacy and toxicities. • It is recommended that follow-up evaluations with patients on amiodarone take place with personnel who are experienced with the agent. • It is recommended that initial assessments occur every three to six months to ensure efficacy and safety of the medication and arrhythmia stability. Following the initial period, follow-up assessments may occur every six months. Pulmonary toxicity • Pulmonary toxicity is a well-known adverse event associated with amiodarone therapy. It is recommended that a pulmonologist be consulted when: 1) there is an abnormal chest radiography at baseline or follow-up; 2) there is an abnormal pulmonary function test value (particularly forced vital capacity and [D_LCO]) at baseline or follow-up evaluation; and/or 3) a new cough and/or dyspnea, especially if otherwise unexplained or unexpected. • It is recommended that all patients who are referred to a pulmonologist undergo full pulmonary function testing and high-resolution computed tomography scanning of the chest. Effects on thyroid function • Amiodarone is known to have adverse effects on thyroid function, either by causing hypo- or hyperthyroidism. It is recommended that an endocrinologist be consulted: 1) any time hyperthyroidism is suspected, even if suppression of thyroid-stimulating hormone is mild and subclinical disease is possible; 2) an acutely ill patient where interpretation of thyroid function tests will be complicated by euthyroid sick syndrome; and/or 3) when considering treating subclinical hypothyroidism. • It is recommended to discontinue amiodarone therapy, if possible, in those patients who have underlying thyroid disease and treat them with high-doses of antithyroid drugs. The decision to discontinue amiodarone therapy should be based on the patient’s cardiac needs. Follow-up visits • A history of complaints from the patient should be noted. In patients with implantable cardioverter-defibrillators, amiodarone therapy should not be altered without the involvement of an electrophysiologist or a cardiologist in charge of device follow-up. • A physical examination with documentation should be performed. If visual changes are reported, an examination by an ophthalmologist is required. • The following are recommended baseline tests that should be performed: liver function tests, thyroid function tests, chest x-ray, ophthalmologic evaluation, pulmonary function tests, high-resolution computed tomography scan, and an electrocardiogram. The follow-up evaluation should include, at minimum, a yearly electrocardiogram and chest x-ray and semiannual thyroid tests and liver enzymes. Amiodarone levels may be obtained after dose adjustments or to help determine if the dose may be decreased. When to refer to an electrophysiologist • Refer when worsening arrhythmia symptoms. • Refer when evidence of amiodarone toxicity requiring changes in drug dosing or drug discontinuation. Until the arrhythmia problem

Clinical Guideline	Recommendation (s)
	stabilizes, the patient may require intensive monitoring, electrophysiologic testing, ablative therapy, or pacemaker or implantable cardioverter-defibrillator implantation. • Repeat defibrillation threshold testing is recommended for patients with an implantable cardioverter-defibrillator due to the drugs effect of increasing this threshold. • Assess amiodarone-induced slowing of ventricular tachyarrhythmias rate in patients with an implantable cardioverter-defibrillator such that ventricular tachyarrhythmias would not be detected by the device and therapy not delivered. • Refer for pregnant patients who require amiodarone. • Refer for pediatric patients who require amiodarone.
American College of Cardiology Foundation/ American Heart Association/Heart Rhythm Society: **Focused Update on the Management of Patients with Atrial Fibrillation (Updating the 2006 Guideline)[4] (2011)[47]**	• With the exception of the recommendations presented in this Focused Update, the full-text guideline remains current. The 2006 guidelines are outlined below.[5] Recommendations for dronedarone for the prevention of recurrent AF • Dronedarone is reasonable to decrease the need for hospitalization for cardiovascular event in patients with paroxysmal AF or after conversion of persistent AF. Dronedarone can be initiated during outpatient therapy. • Dronedarone should not be administered to patients with class IV heart failure or patients who have had an episode of decompensated heart failure in the past four weeks, especially if they have depressed left ventricular function (left ventricular ejection fraction [LVEF] ≤35%).
American College of Cardiology/ American Heart Association/ European Society of Cardiology/Heart Rhythm Society Committee for Practice Guidelines: **Guidelines for the Management of Patients With Atrial Fibrillation[5] (2006)**	Pharmacological rate control during AF • When the ventricular rate cannot be adequately controlled both at rest and during exercise in patients with AF using a β-blocker, nondihydropyridine calcium channel blocker, or digoxin, alone or in combination, oral amiodarone may be administered to control heart rate. • Intravenous procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with AF involving conduction over an accessory pathway. Cardioversion of AF • Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacological cardioversion of AF. • Administration of amiodarone is a reasonable option for pharmacological cardioversion of AF. • A single oral bolus dose of propafenone or flecainide may be used to terminate persistent AF outside the hospital once treatment has proven safe in hospital for selected patients without sinus or atrioventricular node dysfunction, bundle-branch block, QT-interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a β-blocker or nondihydropyridine calcium channel blocker should be given to prevent rapid atrioventricular conduction in the event atrial flutter occurs. • Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not deemed necessary. • Administration of quinidine or procainamide might be considered for pharmacological cardioversion of AF, but the usefulness of these agents is not well established. • Digoxin and sotalol may be harmful when used for pharmacological

Clinical Guideline	Recommendation (s)
	cardioversion of AF and are not recommended. • Quinidine, procainamide, disopyramide, and dofetilide should not be started out of hospital for conversion of AF to sinus rhythm. • Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and prevent recurrent AF. • For patients with persistent AF, administration of β-blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of AF is uncertain. • Out-of-hospital initiation of antiarrhythmic medications may be considered in patients without heart disease to enhance the success of cardioversion of AF. • Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of AF in patients with certain forms of heart disease once the safety of the drug has been verified for the patient. <u>Maintenance of sinus rhythm</u> • Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. • Pharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. • Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. • Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated. • In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation. • Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is <460 msec, serum electrolytes are normal, and risk factors associated with class III drug–related proarrhythmia are not present. • Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well defined risk factors for proarrhythmia with that agent. • Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or atrial ventricular node dysfunction unless they have a functioning electronic cardiac pacemaker. <u>Special considerations</u> • Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for postoperative AF. • It is reasonable to restore sinus rhythm by pharmacological cardioversion with ibutilide in patients who develop postoperative AF as advised for nonsurgical patients. • It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as recommended for other patients who develop AF.

Clinical Guideline	Recommendation (s)
	• Prophylactic administration of sotalol may be considered for patients at risk of developing AF following cardiac surgery. • Administration of quinidine or procainamide may be considered to achieve pharmacological cardioversion in hemodynamically stable patients who develop AF during pregnancy. • Antiarrhythmic medications can be useful to prevent recurrent AF in patients with hypertrophic cardiomyopathy. Available data is insufficient to recommend one agent over another in this situation, but disopyramide combined with a β-blocker or nondihydropyridine calcium channel blocker or amiodarone alone is generally preferred. • In those patients with AF and concurrent obstructive lung disease, therapy with β-blockers, sotalol, propafenone, and adenosine are not recommended.
National Institute for Health and Clinical Excellence: **Dronedarone for the Treatment of Non-permanent Atrial Fibrillation[6] (2010)**	• Dronedarone is recommended as an option for the treatment of non-permanent AF only in the following people: ○ AF is not controlled by first-line therapy (usually including β-blockers). ○ Patients with at least one of the following cardiovascular risk factors: ▪ Hypertension requiring drugs of at least two different classes. ▪ Diabetes. ▪ Previous transient ischemic attack, stroke, or systemic embolism. ▪ Left atrial diameter of 50 mm or greater. ▪ LVEF <40%. ▪ Age ≥70 years. ○ And in patients who do not have New York Heart Association (NYHA) class III or IV heart failure. • Patients who do not meet the above criteria who are currently receiving dronedarone should have the option to continue treatment until they are their clinicians consider it appropriate to stop.
National Institute for Health and Clinical Excellence: **Atrial Fibrillation[7] (2006)**	• Class Ic drugs are the agents of choice for the pharmacological cardioversion of patients with persistent AF and no structural heart disease. • Amiodarone is the drug of choice for pharmacological cardioversion of patients with persistent AF and structural heart disease. • It is recommended that therapy with amiodarone or sotalol be initiated at least four weeks prior to cardioversion in those AF patients who may not be successful at restoring sinus rhythm, such as those who have failed on previous attempts. • The use of antiarrhythmics should be individualized based on the patient's comorbidities, cardiac history and potential risk for side effects. • Appropriate antithrombotic therapy should be used in patients with persistent AF, regardless if they are to receive rhythm control or rate control therapy. • Rhythm control is the recommended initial therapy for patients with AF and the following conditions: symptomatic, young, first presentation of AF, AF due to secondary causes, and/or CHF. • As long as there are no risk factors for recurrence present, therapy with an antiarrhythmic agent is not necessary for sinus rhythm maintenance in those patients who had persistent AF from a secondary cause that has been corrected. • β-blockers are the recommended first-line agents, followed by

Clinical Guideline	Recommendation (s)
	amiodarone as a second-line agent, for the maintenance of sinus rhythm in those patients with persistent AF and structural heart disease. • β-blockers are the recommended first-line agents, followed by a Class Ic agent or sotalol as the second-line agents and amiodarone as the third line agent, for the maintenance of sinus rhythm in those patients with persistent AF without structural heart disease. • β-blockers or rate-limiting calcium channel blockers are the recommended first-line agents for rate control in those patients with permanent AF. Digoxin is only recommended to be used in patients that are predominately sedentary. • In patients who have permanent AF and need therapy to control heart rate during normal activities in addition to the β-blockers or rate-limiting calcium channel blockers, digoxin may be added. • In patients who have permanent AF and need therapy to control heart rate during normal activities and exercise, in addition to the β-blockers or rate-limiting calcium channel blockers, digoxin may be added. • β-blockers are the recommended first-line treatment options, followed by a Class Ic antiarrhythmic agent or sotalol as a second-line agents, followed by amiodarone as a third line agent, for the treatment of symptomatic paroxysms and no structural heart disease. • β-blockers are the recommended first-line treatment option, followed sotalol as a second-line agent, followed by amiodarone as a third line agent, for the treatment of paroxysmal AF and coronary artery disease. • β-blockers are the recommended first-line treatment option, followed by amiodarone as a second-line agent, for the treatment of paroxysmal AF and poor LVEF. • Patients who are receiving medication management for the treatment of their paroxysmal AF should be closely monitored for side effects of therapy. • Intravenous amiodarone should be used in patients with new onset of AF and non life-threatening hemodynamic instability where electrical cardioversion is delayed. • Flecainide may be used to cardiovert patients with Wolff–Parkinson–White syndrome and non life-threatening hemodynamic instability. It is recommended not to use diltiazem, verapamil, or digoxin to cardiovert these patients. • In those patients who have poorly controlled ventricular rates causing hemodynamic instability, it is recommended to use a pharmacological rate-control strategy for treatment. • Intravenous β-blockers or rate-limiting calcium channel blockers are the recommended first-line agents, followed by amiodarone as a second-line agent for urgent rate control. • Amiodarone, β-blockers, sotalol, or rate-limiting calcium channel blockers are recommended agents to prevent postoperative AF in those patients undergoing cardiothoracic surgery. Digoxin is not recommended in this specific situation. • Patients receiving β-blocker therapy prior to cardiothoracic surgery should continue their therapy unless indicated otherwise. • Rhythm control is the recommend initial therapy regimen for patients following cardiothoracic unless contraindications are present. • Patients should have a follow-up visit with their health care practitioner at one and six months post successful cardioversion to assess maintenance of sinus rhythm.
American College of	Drug therapy for ventricular arrhythmias

Clinical Guideline	Recommendation (s)
Cardiology/American Heart Association/ European Society of Cardiology Committee for Practice Guidelines: **Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[8] (2006)**	• β-blockers are currently the mainstay of pharmacologic therapy for the treatment of arrhythmias, due to their safety profile and effectiveness. • Other than β-blockers, alternative antiarrhythmic agents currently available have not been proven effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of sudden cardiac death. • For patients that are arrhythmia-prone, antiarrhythmic agents may be effective as adjunctive therapy in particular situations. • Caution should be used when any antiarrhythmic agent is used for therapy, as there are many side effects associated with these agents. • β-blockers, or alternatively, amiodarone or sotalol, may be used in patients with ventricular tachycardia who do not meet criteria for an implantable cardioverter-defibrillator. • Sotalol or, alternatively the combination of β-blockers and amiodarone, may be used in patients with implantable cardioverter-defibrillators who have recurrent ventricular tachycardia/ventricular fibrillation with frequent appropriate implantable cardioverter-defibrillator firing. <u>Ventricular arrhythmia and sudden cardiac death related to specific pathology</u> Left ventricular dysfunction due to prior MI: • Amiodarone, often in combination with β-blockers, can be useful for patients with left ventricular dysfunction due to prior MI and symptoms due to ventricular tachycardia unresponsive to β-blocking agents. • Sotalol is reasonable therapy to reduce symptoms resulting from ventricular tachycardia for patients with left ventricular dysfunction due to prior MI unresponsive to β-blocking agents. • Alternative therapies to the implantable cardioverter-defibrillator to improve symptoms due to frequent episodes of sustained ventricular tachycardia or ventricular fibrillation in patients with left ventricular dysfunction due to prior MI include agents such as amiodarone or sotalol. • To reduce symptoms in patients due to recurrent hemodynamically stable ventricular tachycardia with left ventricular dysfunction due to prior MI and who cannot or refuse to have an implantable cardioverter-defibrillator implanted, amiodarone may be used as an alternative therapy. • To improve symptoms in patients with left ventricular dysfunction due to prior MI and recurrent hemodynamically stable ventricular tachycardia whose LVEF is >40% and an implantable cardioverter-defibrillator is not appropriate, amiodarone may be considered an alternative treatment option. • In patients with left ventricular dysfunction due to prior MI where an implantable cardioverter-defibrillator is indicated but is not appropriate or desired by the patient, amiodarone may be considered an alternative treatment option. • Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. • Class Ic antiarrhythmic agents are not recommended in patients with a past history of MI. Congenital heart disease: • Prophylactic antiarrhythmic therapy is not indicated for asymptomatic

Clinical Guideline	Recommendation (s)
	patients with congenital heart disease and isolated premature ventricular contractions. Metabolic and inflammatory conditions: • Antiarrhythmic therapy can be useful in patients with symptomatic non-sustained ventricular tachycardia or sustained ventricular tachycardia during the acute phase of myocarditis. Pericardial disease: • Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of sudden cardiac death in patients with pulmonary arterial hypertension or other pulmonary conditions. <u>Ventricular arrhythmias associated with cardiomyopathies</u> Dilated cardiomyopathy (nonischemic): • Amiodarone may be considered for sustained ventricular tachycardia or ventricular fibrillation in patients with nonischemic dilated cardiomyopathy. <u>Hypertrophic cardiomyopathy</u> • Amiodarone therapy can be effective for treatment in patients with hypertrophic cardiomyopathy with a history of sustained ventricular tachycardia and/or ventricular fibrillation when implantable cardioverter-defibrillator is not feasible. • Amiodarone may be considered for primary prophylaxis against sudden cardiac death in patients with hypertrophic cardiomyopathy who have one or more major risk factor for sudden cardiac death, if implantable cardioverter-defibrillator implantation is not feasible. <u>Arrhythmogenic right ventricular cardiomyopathy</u> • Amiodarone or sotalol can be effective for treatment of sustained ventricular tachycardia or ventricular fibrillation in patients with arrhythmogenic right ventricular cardiomyopathy when implantable cardioverter-defibrillator implantation is not feasible. <u>Heart failure</u> • Amiodarone, sotalol and/or other β-blockers are recommended pharmacological adjuncts to implantable cardioverter-defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with heart failure. • Amiodarone is indicated for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence. • Amiodarone, sotalol, and/or β-blockers may be considered as pharmacological alternatives to implantable cardioverter-defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with heart failure for whom implantable cardioverter-defibrillator therapy is not feasible. <u>Genetic arrhythmia syndromes</u> Long QT syndrome: • β-blockers are recommended for patients with a long QT syndrome clinical diagnosis (i.e., in the presence of prolonged QT interval).

Clinical Guideline	Recommendation (s)
	• Implantation of an implantable cardioverter-defibrillator along with use of β-blockers is recommended for long QT syndrome patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than one year. • β-blockers can be effective to reduce sudden cardiac death in patients with a molecular long QT syndrome analysis and normal QT interval. • Implantation of an implantable cardioverter-defibrillator with continued use of β-blockers can be effective to reduce sudden cardiac death in long QT syndrome patients experiencing syncope and/or ventricular tachycardia while receiving β-blockers and who have reasonable expectation of survival with a good functional status for more than one year. Short QT syndrome and Brugada syndrome: • Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. Catecholaminergic polymorphic ventricular tachycardia: • β-blockers are indicated for patients who are clinically diagnosed with catecholaminergic polymorphic ventricular tachycardia on the basis of the presence of spontaneous or documented stress-induced ventricular arrhythmias. • β-blockers can be effective in patients without clinical manifestations when the diagnosis of catecholaminergic polymorphic ventricular tachycardia is established during childhood based on genetic analysis. • β-blockers may be considered for patients with catecholaminergic polymorphic ventricular tachycardia who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. <u>Arrhythmias in structurally normal hearts</u> Idiopathic ventricular tachycardia: • Drug therapy with β-blockers and/or calcium channel blockers can be useful in patients with structurally normal hearts with symptomatic ventricular tachycardia arising from the right ventricle. <u>Ventricular arrhythmias and sudden cardiac death related to specific populations</u> Pregnancy: • In pregnant women with the long QT syndrome who have had symptoms, it is beneficial to continue β-blocker medications throughout pregnancy and afterward, unless there are definite contraindications. Elderly: • The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients.
American College of Chest Physicians: **Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery[9] (2005)**	• β-blockers and nondihydropyridine calcium channel blockers are recommended as first and second-line agents to control ventricular response rate in AF after cardiac surgery. • Agents with proarrhythmic properties and those that are contraindicated in patients with coronary artery disease have not been shown to be effective in controlling the ventricular response rate in AF after cardiac surgery.

Clinical Guideline	Recommendation (s)
	• Amiodarone is the recommended first-line agent for pharmacologic rhythm control of postoperative AF or atrial flutter in patients with depressed left ventricular function who do not need urgent electrical cardioversion. • Sotalol and Class Ia antiarrhythmics are the recommended first-line agents for pharmacologic rhythm control of postoperative AF or atrial flutter in patients with coronary artery disease without CHF. • When prophylaxis to prevent postoperative AF is indicated, β-blockers are the recommended agents. • Sotalol may be an alternative therapy to prevent postoperative AF, but its ability to cause toxicity may not make it a favorable option. • Amiodarone may also be considered as an alternative therapy to β-blockers to prevent postoperative AF, but its ability to cause toxicity may not make it a favorable option.
American Academy of Family Physicians/American College of Physicians: **Management of Newly Detected Atrial Fibrillation[10] (2003)**	• The recommendations provided in this guideline do not apply to the following patients: those with postoperative or post-MI AF, those with NYHA Class IV heart failure, those already taking antiarrhythmic drugs, or those with valvular disease. • For the treatment of AF, rate control (with chronic anticoagulation) is the recommended first-line treatment strategy in the majority of patients. Due to the lack of efficacy shown in clinical trials in reducing morbidity and mortality, rhythm control should be reserved for occasions when necessary, such as patient symptoms, exercise tolerance, and patient preference. • Atenolol, metoprolol, diltiazem and verapamil are the recommended agents of choice for the treatment of AF who require rate control at rest and during exercise. • Digoxin may be used as a second-line agent for those patients with AF who require rate control at rest. • Pharmacological cardioversion is an appropriate treatment option for patients who elect to undergo acute cardioversion to achieve sinus rhythm. • Agents that have been shown to be effective during pharmacological cardioversion of AF include ibutilide, flecainide, dofetilide, propafenone, and amiodarone. Quinidine also has some moderate evidence to support its use for pharmacological cardioversion of AF. Due to the lack of safety data, the American Academy of Family Physicians/American College of Physicians has not made recommendations regarding the setting of cardioversion. • Due to the risks associated with rhythm maintenance therapy, it is not recommended to convert a majority of AF patients to sinus rhythm. Rhythm maintenance therapy may be appropriate during certain circumstances, including in those patients whose quality of life is affected by AF. The agents that are recommended for rhythm maintenance include amiodarone, disopyramide, propafenone, and sotalol. The agent should be chosen based on patient specific characteristics. • For patients with congestive systolic heart failure and left ventricular hypertrophy, amiodarone is considered one of the safer agents recommended. • In patients with coronary artery disease, sotalol and amiodarone are considered to be the safest recommended agents.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antiarrhythmic agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Antiarrhythmic Agents[11-19]

Indication	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Atrial Arrhythmias								
Chronic therapy in patients at high risk of symptomatic atrial fibrillation (AF)/flutter								✔ *
Conversion of AF and atrial flutter to normal sinus rhythm			✔					
Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter) in patients with AF/atrial flutter of greater than one week duration who have been converted to normal sinus rhythm			✔ †					
Prevention of paroxysmal atrial fibrillation/flutter (PAF) associated with disabling symptoms and paroxysmal supraventricular tachycardias (PSVT) associated with disabling symptoms in patients without structural heart disease					✔			
Prolong the time to recurrence of symptomatic AF in patients without structural heart disease							✔ ‡	
Prolong the time to recurrence of PAF and PSVT associated with disabling symptoms in patients without structural heart disease							✔ §	
Reduce the risk of hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF				✔				

Indication	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Restore normal sinus rhythm in patients with symptomatic AF/atrial flutter whose symptoms are not adequately controlled by measures that reduce the rate of ventricular response								✔
Ventricular Arrhythmias								
Initiation of treatment and prophylaxis of frequently ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy	✔ (Nexterone®)‖							
Prevention of life-threatening ventricular arrhythmias (e.g., sustained VT)					✔			
Suppression of recurrent life-threatening ventricular arrhythmias (e.g., sustained VT)								✔
Treatment of life-threatening ventricular arrhythmias (e.g., sustained VT)		✔				✔	✔ §	
Treatment of recurrent VF	✔ ¶ (Cordarone®, Pacerone®)							
Treatment of recurrent hemodynamically unstable VT	✔ ¶ (Cordarone®, Pacerone®)							
Miscellaneous								
Treatment of life-threatening *Plasmodium falciparum* malaria								✔

*This includes patients who have had previous episodes of atrial fibrillation/flutter that were so frequent and poorly tolerated as to outweigh, in the judgment of the physician and the patient, the risks of prophylactic therapy with quinidine sulfate. The increased risk of death should specifically be considered. Quinidine sulfate should be used only after alternative measures (e.g., use of other drugs to control the ventricular rate) have been found to be inadequate.
†Because dofetilide can cause life threatening ventricular arrhythmias, it should be reserved for patients in whom atrial fibrillation/atrial flutter is highly symptomatic.
‡Sustained-release formulation.
§Immediate-release formulation.
‖Nextrone® can also be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medications. During or after treatment with Nextrone®, patients may be transferred to oral amiodarone therapy. Use Nextrone® for acute treatment until patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48 to 96 hours, but Nextrone® may be safely administered for longer periods if necessary.
¶ Because of its life-threatening side effects and the substantial management difficulties associated with its use, amiodarone is indicated only for the treatment of the life-threatening recurrent ventricular arrhythmias when these have not responded to documented adequate doses of other available antiarrhythmics or when alternative agents could not be tolerated.

IV. Pharmacokinetics

The pharmacokinetic parameters of the antiarrhythmic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antiarrhythmic Agents[20]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Amiodarone	35 to 65	96	Liver (% not reported; extensive)	Renal (<1) Bile (% not reported; primary)	26 to 107 days
Disopyramide	80	50 to 65	Liver (45)	Renal (40 to 80) Feces (15)	4 to 10 hours
Dofetilide	>90	60 to 70	Liver (50)	Renal (80) Feces (<10)	7.5 to 10 hours
Dronedarone	15	>98	Liver (% not reported; extensive)	Renal (6) Feces 84)	13 to 19 hours
Flecainide	70 to 95	40	Liver (% not reported; extensive)	Renal (81 to 90) Feces (4 to 6)	7 to 22 hours
Mexiletine	80 to 90	50 to 70	Liver (% not reported; extensive)	Renal (8 to 15)	6 to 17 hours
Propafenone	12	85 to 97	Liver (% not reported; extensive)	Renal (<1) Feces (53)	5 to 8 hours
Quinidine	70 to 80 (oral)	80 to 90	Liver 50 to 90)	Renal (17 to 50) Feces (1 to 3)	6 to 8 hours

V. Drug Interactions

Significant drug interactions with the antiarrhythmic agents are listed in Table 5.

Table 5. Significant Drug Interactions with the Antiarrhythmic Agents[19]

Generic Name(s)	Significance Level	Interaction	Mechanism
Amiodarone, Disopyramide, Flecainide, Propafenone, Quinidine	1	Cisapride	Possible additive prolongation of the QT interval, increasing the risk of life-threatening cardiac arrhythmias.
Amiodarone, Disopyramide, Dofetilide, Flecainide, Propafenone, Quinidine	1	Dronedarone	Possible additive or synergistic prolongation of the QT interval, increasing the risk of life-threatening cardiac arrhythmias.
Amiodarone	1	Digoxin	Amiodarone may increase the oral bioavailability and decrease the systemic clearance of digoxin; additional mechanisms may exist. Mechanism of interaction is unknown but it is thought that multiple mechanisms are involved.
Amiodarone	1	Fentanyl	Mechanism of interaction is unknown. Profound bradycardia, sinus arrest, and hypotension have occurred with concurrent

Generic Name(s)	Significance Level	Interaction	Mechanism
			administration.
Amiodarone	1	HMG-CoA reductase inhibitors	Amiodarone may inhibit the metabolism of HMG-CoA reductase inhibitors (cytochrome P450 [CYP] 3A4) thereby increasing plasma concentrations and increasing the risk of toxicity.
Amiodarone, Disopyramide, Dofetilide, Dronedarone, Quinidine	1	Macrolide and related antibiotics	An additive or synergistic increase in the QT interval may result, increasing the risk of life-threatening cardiac arrhythmias.
Amiodarone, Disopyramide, Dofetilide, Dronedarone, Quinidine	1	Phenothiazines	Concurrent use may lead to the prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Amiodarone, Dronedarone	1	Protease inhibitors	Protease inhibitors may inhibit the metabolism (CYP3A4) of certain antiarrhythmics, thereby increasing antiarrhythmic concentrations and increasing the risk of toxicity.
Amiodarone	1	Quinidine	Mechanism of interaction is unknown. Concurrent therapy may lead to an increase in quinidine concentrations and produce potentially fatal cardiac dysrhythmias.
Amiodarone, Disopyramide, Dofetilide, Quinidine	1	Quinolones	Concurrent use of these agents may lead to additive prolongation of the QT interval which may increase the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Amiodarone, Disopyramide	1	Vardenafil	Mechanism of interaction is unknown. The risk of life-threatening cardiac arrhythmias may be increased with concurrent use.
Amiodarone	1	Warfarin	Amiodarone inhibits the metabolism (CYP1A2 and CYP2C9) of the R- and S-enantiomers of warfarin; therefore the hypoprothrombinemic effects may be augmented.
Amiodarone, Disopyramide, Dofetilide, Quinidine	1	Ziprasidone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility with concurrent administration.
Dofetilide, Quinidine	1	Azole antifungals	Certain azole antifungal agents may inhibit the metabolism (CYP3A4) and active renal secretion of dofetilide or quinidine. Plasma dofetilide or quinidine concentrations may be elevated, increasing the risk of serious cardiovascular events.
Dofetilide	1	Cimetidine	Cimetidine may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	1	Megestrol	Concurrent use results in inhibition of the

Generic Name(s)	Significance Level	Interaction	Mechanism
			renal cation transport system responsible for dofetilide elimination, increasing the risk of ventricular arrhythmias.
Dofetilide	1	Thiazide diuretics	Thiazide diuretics may increase potassium excretion causing hypokalemia which may increase the risk of torsades de pointes.
Dofetilide	1	Trimethoprim	Trimethoprim may increase dofetilide concentrations by inhibiting the renal cation transport system, which is responsible for dofetilide elimination. Elevated dofetilide concentrations may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dofetilide	1	Verapamil	Verapamil may increase the rate of dofetilide absorption by increasing portal blood flow thereby increasing dofetilide plasma concentrations which may increase the risk of ventricular arrhythmias, including torsades de pointes.
Dronedarone	1	Azole antifungal agents	Dronedarone plasma concentrations may be elevated, increasing the risk of toxicity, including life-threatening cardiotoxicity.
Dronedarone	1	Cyclosporine	Dronedarone plasma concentrations may be elevated, increasing the risk of toxicity, including life-threatening cardiotoxicity.
Dronedarone	1	Nefazodone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by nefazodone. Inhibition of CYP3A by nefazodone may decrease the metabolic elimination of dronedarone.
Dronedarone	1	Tricyclic antidepressants	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Flecainide	1	Ritonavir	Large increases in serum flecainide concentrations may occur, increasing the risk of flecainide toxicity.
Mexiletine	1	Tizanidine	Tizanidine plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Propafenone	1	Digoxin	Mechanism of interaction is unknown. Serum digoxin levels may be increased, resulting in toxicity.
Propafenone	1	Ritonavir	Large increases in serum propafenone concentrations may occur, increasing the risk of propafenone toxicity.
Quinidine	1	Digoxin	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.
Quinidine	1	Mifepristone	Quinidine plasma concentrations may be elevated due to inhibition of metabolism by mifepristone, increasing the pharmacologic effects and risk of adverse reactions
Quinidine	1	Protease inhibitors	Protease inhibitors may inhibit the metabolism (CYP3A4) of quinidine. Large increases in serum quinidine concentrations

Generic Name(s)	Significance Level	Interaction	Mechanism
			may occur, increasing the risk of quinidine toxicity.
Quinidine	1	Verapamil	Verapamil may decrease the clearance of quinidine and prolong its half-life which may lead to hypotension, bradycardia, ventricular tachycardia and atrioventricular block.
Quinidine	1	Warfarin	Quinine derivatives also may inhibit the hepatically synthesized clotting factors. Anticoagulation may be potentiated by quinine derivatives and hemorrhage may occur.
Amiodarone	2	Cyclosporine	Mechanism of the interaction is unknown. Amiodarone may inhibit the metabolism of cyclosporine which may lead to an increase in cyclosporine blood concentrations, possibly increasing the risk of nephrotoxicity.
Amiodarone	2	Flecainide	Amiodarone may decrease the metabolism of flecainide and plasma levels may be increased.
Amiodarone, Mexiletine, Quinidine	2	Hydantoins	Phenytoin may increase the hepatic metabolism of certain antiarrhythmics via stimulation of microsomal enzymes.
Amiodarone	2	Procainamide	Mechanism of the interaction is unknown. Amiodarone may increase serum concentrations of procainamide.
Disopyramide, Quinidine	2	Hydantoins	Phenytoin appears to increased hepatic metabolism of disopyramide via stimulation of microsomal enzymes.
Disopyramide	2	Rifampin	Hepatic metabolism of disopyramide is increased with concurrent use.
Dronedarone	2	Digoxin	Plasma concentrations and pharmacologic effects of digoxin may be increased, due to inhibition of P-glycoprotein efflux transport.
Flecainide	2	Amiodarone	Flecainide plasma levels may be increased.
Mexiletine	2	Propafenone	Mexiletine plasma concentrations may be elevated in extensive metabolizers, increasing the risk of side effects.
Mexiletine	2	Theophylline	Mexiletine may impair hepatic elimination and increase plasma concentrations of theophylline. Additive arrhythmogenic effects may also occur.
Propafenone	2	β-blockers	The pharmacologic effects of beta-blockers metabolized by the liver may be increased.
Propafenone	2	Quinidine	Serum propafenone levels may be increased in rapid, extensive metabolizers of the drug (≈ 90% of the patients), increasing the pharmacologic effects of propafenone.
Propafenone	2	Serotonin reuptake inhibitors	Propafenone plasma concentrations may be increased by serotonin-norepinephrine reuptake inhibitors, due to inhibition of cytochrome CYP2D6 isoenzymes.
Propafenone, Quinidine	2	Rifamycins	Rifamycins may induce the hepatic microsomal enzymes responsible for metabolizing certain antiarrhythmics, whose increased clearance may lead to a decrease in

Generic Name(s)	Significance Level	Interaction	Mechanism
			plasma levels and a possible loss of therapeutic effects.
Quinidine	2	Antacids	Certain antacids may increase serum quinidine concentrations, which may result in toxicity.
Quinidine	2	Anti-cholinesterases	Quinidine derivatives may reverse the effects of anticholinesterases and vice versa.
Quinidine	2	Aripiprazole	Quinidine may inhibit the hepatic metabolism (CYP2D6) of aripiprazole thereby increasing plasma concentrations and potentiating the pharmacologic effects and adverse reactions.
Quinidine	2	Barbiturates	Barbiturates may increase the metabolic clearance of quinidine thereby decreasing quinidine serum concentrations and elimination half-life.
Quinidine	2	β-blockers	Quinidine may inhibit the oxidative metabolism of certain beta-blockers. The effects of certain β-blockers may be increased in "extensive metabolizers."
Quinidine	2	Cimetidine	Inhibition of hepatic microsomal enzymes by cimetidine may decrease the metabolic elimination of quinidine. Additional mechanisms may exist including a decrease in renal clearance of quinidine possibly due to competition with cimetidine for renal tubular secretion.
Quinidine	2	Codeine	Quinidine may decrease pharmacologic effects of codeine, due to inhibition of CYP2D6 isoenzymes and thereby decreased metabolic conversion of codeine to morphine. Loss of analgesic effect may occur.
Quinidine	2	Diltiazem	The therapeutic and adverse effects of quinidine may be increased due to inhibition of the hepatic metabolism of quinidine by competition for the same isozyme.
Quinidine	2	Nifedipine	Plasma concentrations and pharmacologic effects of quinidine may be decreased by nifedipine. Plasma concentrations and pharmacologic effects of nifedipine may be increased by quinidine, which may decrease the first-pass metabolism of nifedipine by inhibiting aromatization.
Quinidine	2	Non-depolarizing muscle relaxants	Concurrent use of these agents may cause synergistic pharmacologic effects. Non-depolarizing muscle relaxants effects may be enhanced by quinine and quinine derivatives.
Quinidine	2	Succinylcholine	Quinidine may produce a decrease in plasma cholinesterase activity resulting in a slowed metabolic rate for succinylcholine. The neuromuscular blockade produced by succinylcholine may be prolonged.

Significance Level 1 = major severity.
Significance Level 2 = moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the antiarrhythmic agents are listed in Table 6. The boxed warnings for the antiarrhythmic agents are listed in Tables 7 through 12.

Table 6. Adverse Drug Events (%) Reported with the Antiarrhythmic Agents[11-20]

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Cardiovascular								
Alters pacing threshold	-	-	-	-	<1	-	-	-
Angina	-	-	-	-	<1	2	2 to 5	6
Arrhythmia	1 to 10	-	-	-	-	-	-	1 to 10
Asystole	1 to 10	-	-	-	-	-	-	-
Atrial fibrillation	-	-	-	-	-	-	1	-
AV block	5	<1	0.4 to 1.5	-	<1	<1	1 to 3	-
AV dissociation	-	-	-	-	-	-	<1	-
Bradycardia	3 to 5	-	-	3	<1	-	1 to 2	<1
Bundle branch block	-	-	<2	-	-	-	0-1	-
Cardiac arrest	1 to 10	-	<2	-	-	-	<1	-
Cardiogenic shock	1 to 10	-	-	-	-	<1	-	-
Chest pain	-	1 to 10	10	-	5	3 to 8	1 to 2	-
Conduction abnormalities	1 to 10	1 to 10	-	-	-	-	0 to 1	-
Congestive heart failure	-	1 to 10	-	-	-	-	-	-
Edema	1 to 10	1 to 10	-	✔	3.5	-	0 to 1	-
Electromechanical dissociation	1 to 10	-	-	-	-	-	-	-
Heart block	-	-	<2	-	<1	-	-	<1
Hypertension	-	-	-	-	-	-	0 to 1	-
Hypotension	<1	1 to 10	-	-	-	<1	-	✔
Myocardial infarction	-	-	<2	-	-	-	-	-
Palpitations	-	-	-	-	6	4 to 8	1 to 3	7
Premature ventricular contractions	-	-	-	-	-	1 to 2	1 to 2	-
Proarrhythmia	<1	<1	-	-	4 to 12	10 to 15	2 to 10	-
P-R increased	-	-	-	-	<1	-	-	-
QRS duration	-	-	-	-	<1	-	1 to 2	-
QT interval increased	<1	-	-	-	-	-	-	>10
QTc prolonged	-	-	-	28	-	-	-	-
SA node dysfunction	1 to 3	-	-	-	-	-	-	-
Sinus arrest	<1	-	-	-	-	<1	-	-
Sinus node dysfunction	-	-	-	-	1.2	-	<1	-
Stroke	-	-	<2	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Tachycardia	-	-	-	-	1 to 3	-	-	<1
Torsades de pointes	<1	-	0.9 to 10.5	-	-	<1	-	<1
Ventricular arrhythmia	-	-	-	-	<1	-	-	-
Ventricular fibrillation	<1	-	0 to 0.4	-	-	-	-	<1
Ventricular rate increase	-	-	-	-	<1	-	-	<1
Ventricular tachycardia	1 to 10	-	2.6 to 3.7	-	-	-	1 to 3	<1
Central Nervous System								
Abnormal gait/ataxia	3 to 40	-	-	-	-	-	-	-
Amnesia	-	-	-	-	<1	-	<1	-
Anxiety	-	-	-	-	1 to 3	-	1 to 2	-
Ataxia	-	-	-	-	1 to 3	10 to 20	0 to 2	-
Cerebral hypoperfusion	-	-	-	-	-	-	-	<1
Coma	-	-	-	-	-	-	<1	-
Confusion	<1	-	-	-	-	1 to 10	<1	<1
Delirium	-	-	-	-	-	-	-	<1
Depersonalization	-	-	-	-	<1	-	-	-
Depression	-	<1	-	-	1 to 3	2	<1	<1
Disorientation	<1	-	-	-	-	-	-	-
Dizziness	3 to 40	1 to 10	8	-	19 to 30	20 to 25	4 to 15	-
Drowsiness	-	-	-	-	-	-	1	-
Encephalopathy	<1	-	-	-	-	-	-	-
Euphoria	-	-	-	-	<1	-	-	-
Fatigue	3 to 40	1 to 10	-	-	8	-	2 to 6	7
Fever	-	-	-	-	1 to 3	-	-	<1
Flushing	-	-	-	-	-	-	-	<1
Hallucinations	<1	-	-	-	-	<1	-	<1
Headache	3 to 40	1 to 10	11	-	4 to 10	1 to 10	2 to 5	7
Impaired memory	3 to 40	-	-	-	-	-	-	-
Insomnia	3 to 40	<1	4	-	1 to 3	5 to 7	0 to 2	-
Involuntary movement	3 to 40	-	-	-	-	-	-	-
Lightheadedness	-	-	-	-	-	11 to 25	-	15
Malaise	3 to 40	1 to 10	-	-	1 to 3	-	-	-
Memory loss	-	-	-	-	-	-	<1	-
Nervousness	-	1 to 10	-	-	5	5 to 10	-	2
Paresis	-	-	-	-	1 to 3	-	-	-
Peripheral neuropathy	3 to 40	-	-	-	-	-	-	-
Poor coordination	3 to 40	-	-	-	-	10	-	1

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Psychotic reaction/psychosis	-	<1	-	-	-	<1	<1	<1
Seizure	-	-	-	-	-	<1	0.3	-
Sleep disturbances	3 to 40	-	-	-	-	-	-	3
Somnolence	-	-	-	-	1 to 3	-	-	-
Syncope	-	1 to 10	<2	-	1 to 10	<1	1 to 2	1 to 8
Tardive dyskinesia	-	-	-	-	<1	-	-	-
Vertigo	-	-	-	-	1 to 3	-	<1	<1
Visual disturbances	<10	-	-	-	16	-	-	<1
Dermatological								
Abnormal pigmentation	-	-	-	-	-	-	-	<1
Allergic dermatitis	-	-	-	≤5	-	-	-	-
Alopecia	<1	-	-	-	<1	<1	<1	-
Eczematous dermatitis	-	-	-	≤5	-	-	-	<1
Epididymitis	<1	-	-	-	-	-	-	-
Erythema multiforme	<1	-	-	-	-	-	-	-
Exfoliative dermatitis	<1	-	-	-	<1	<1	-	<1
Flushing	1 to 10	-	-	-	-	-	-	-
Generalized dermatoses	-	1 to 10	-	-	-	-	-	-
Leukocytoclastic vasculitis	<1	-	-	-	-	-	-	-
Lichen planus	-	-	-	-	-	-	-	<1
Livedo reticularis	-	-	-	-	-	-	-	<1
Melanin pigmentation of hard palate	-	-	-	-	-	-	-	<1
Phlebitis	1 to 10	-	-	-	-	-	-	-
Photophobia	<1	-	-	-	<1	-	-	-
Photosensitivity	10 to 75	-	-	<1	-	-	-	<1
Pruritus	<1	1 to 10	-	≤5	<1	-	<1	<1
Purpura	-	-	-	-	-	-	<1	-
Rash	<1	1 to 10	3	≤5	1 to 3	4	1 to 3	5
Slate blue skin discoloration	<10	-	-	-	-	-	-	-
Spontaneous ecchymosis	<1	-	-	-	-	-	-	-
Stevens-Johnson syndrome	<1	-	-	-	-	<1	-	-
Toxic cutaneous blisters	-	<1	-	-	-	-	-	-
Toxic epidermal necrolysis	<1	-	-	-	-	-	-	-
Urticaria	-	-	-	-	<1	<1	-	<1
Vasculitis	<1	-	-	-	-	-	-	-
Endocrine and Metabolic								
Decreased libido	1 to 10	-	-	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Erectile dysfunction	<1	-	-	-	-	-	-	-
Gynecomastia	-	<1	-	-	-	-	-	-
Hyperthyroidism	3 to 10	-	-	-	-	-	-	-
Hypothyroidism	1 to 22	-	-	-	-	-	-	-
Impotence	<1	1 to 3	-	-	-	<1	<1	-
Gastrointestinal								
Abdominal bloating	-	1 to 10	-	-	-	-	-	-
Abdominal distention	-	1 to 10	-	-	-	-	-	-
Abdominal pain	1 to 10	-	3	4	3	1	1 to 2	-
Abnormal salivation	1 to 10	-	-	-	-	-	-	-
Abnormal taste	1 to 10	-	-	-	<1	-	3 to 23	>10
Angioedema	<1	-	<2	-	-	-	-	<1
Anorexia	10 to 33	1 to 10	-	-	1 to 3	-	1 to 2	>10
Cholestasis	-	-	-	-	-	-	0.1	-
Constipation	10 to 33	11	-	-	1	4 to 5	2 to 7	-
Diarrhea	-	1 to 10	3	9	0.7 to 3.0	4 to 5	1 to 3	35
Dry throat	-	1 to 10	-	-	-	-	-	-
Dysgeusia	-	-	-	<1	-	-	-	-
Dyspepsia	-	-	-	2	-	-	1 to 3	-
Dysphagia	-	-	-	-	-	<1	-	-
Esophagitis	-	-	-	-	-	-	-	<1
Flatulence	-	1 to 10	-	-	-	-	0 to 1	-
Gastrointestinal distress	-	-	-	-	-	41	-	>10
Nausea	10 to 33	1 to 10	5	5	9	40	2 to 11	>10
Stomach cramping	-	-	-	-	-	-	-	22
Swollen lips/tongue/mouth	-	-	-	-	<1	-	-	-
Upper gastrointestinal bleeding	-	-	-	-	-	<1	-	-
Vomiting	10 to 33	1 to 10	-	2	-	40	2 to 11	>10
Weight gain	-	1 to 10	-	-	-	-	-	-
Xerostomia	-	32	-	-	-	3	1 to 2	-
Genitourinary								
Urinary frequency	-	1 to 10	-	-	-	-	-	-
Urinary hesitancy	-	14 to 23	-	-	-	-	-	-
Urinary retention	-	1 to 10	-	-	<1	<1	-	-
Urinary urgency	-	1 to 10	-	-	-	-	-	-
Hematological								
Agranulocytosis	<1	<1	-	-	-	<1	<1	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Aplastic anemia	<1	-	-	-	-	-	-	-
Coagulation abnormalities	1 to 10	-	-	-	-	-	-	-
Granulocytopenia	-	-	-	-	<1	-	<1	-
Hemolytic anemia	<1	-	-	-	-	-	-	<1
Hemoptysis	<1	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	<1	<1	<1	-
Neutropenia	<1	-	-	-	-	-	-	-
Pancytopenia	<1	-	-	-	-	-	-	<1
Thrombocytopenia	<1	<1	-	-	<1	<1	<1	<1
Hepatic								
AST or ALT level >2x normal	15 to 50	<1	-	-	-	-	-	-
Cirrhosis	<3	-	-	-	-	-	-	-
Hepatic necrosis	-	-	-	-	-	<1	-	-
Hepatitis	<3	-	-	-	-	<1	0.03	<1
Hepatotoxicity	-	<1	<2	-	-	-	-	<1
Laboratory Test Abnormalities								
Hypercholesterolemia	-	1 to 10	-	-	-	-	-	-
Hyperglycemia	<1	-	-	-	-	-	<1	-
Hypertriglyceridemia	<1	1 to 10	-	-	-	-	-	-
Hypoglycemia	-	<1	-	-	-	-	-	-
Hypokalemia	-	1 to 10	-	✔	-	-	-	-
Hypomagnesemia	-	-	-	✔	-	-	-	-
Serum creatinine increased	-	<1	-	51	-	-	-	-
Musculoskeletal								
Arthralgia	-	-	-	-	-	1	0 to 1	<1
Back pain	-	-	3	-	-	-	-	-
Facial paralysis	-	-	<2	-	-	-	-	-
Flaccid paralysis	-	-	<1	-	-	-	-	-
Lupus	-	<1	-	-	-	<1	<1	-
Lupus-like syndrome	-	-	-	-	-	-	-	<1
Muscle pain (myalgia)	-	1 to 10	-	-	-	-	-	<1
Myopathy	<1	-	-	-	-	-	-	-
Neuropathy	-	<1	-	-	<1	2 to 4	<1	-
Paralysis	-	-	<2	-	-	-	-	-
Paresthesia	-	<1	<2	-	1	2	<1	-
Parkinsonian symptoms	<1	-	-	-	-	-	-	-
Rhabdomyolysis	<1	-	-	-	-	-	-	-

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Trembling	-	-	-	-	-	>10	-	-
Tremor	3 to 40	-	-	-	5	13	0 to 1	2
Unsteady gait	-	-	-	-	-	>10	-	-
Weakness	<1	1 to 10	-	7	5	5	1 to 2	5
Ocular								
Blurred vision	-	1 to 10	-	-	1 to 10	5 to 7	1 to 6	1 to 10
Corneal micro-deposits	>90	-	-	-	<1	-	-	-
Diplopia	-	-	-	-	1 to 3	-	-	-
Dry eyes	-	1 to 10	-	-	-	-	-	-
Halo vision	<5	-	-	-	-	-	-	-
Mydriasis	-	-	-	-	-	-	-	<1
Nystagmus	-	-	-	-	-	6	-	-
Optic neuritis	1	-	-	-	-	-	-	<1
Optic neuropathy	<1	-	-	-	-	-	-	-
Uveitis	-	-	-	-	-	-	-	<1
Visual disturbances	2 to 9	-	-	-	-	-	-	-
Renal								
Acute renal failure	<1	-	-	-	-	-	<1	-
Nephropathy	-	-	-	-	-	-	-	<1
Nephrotic syndrome	-	-	-	-	-	-	<1	-
Respiratory								
Acute respiratory distress syndrome	2	-	-	-	-	-	-	-
Alveolar pneumonitis	✔	-	-	-	-	-	-	-
Apnea	-	-	-	-	-	-	<1	-
Bronchiolitis obliterans organizing pneumonia	<1	-	-	-	-	-	-	-
Bronchospasm	<1	-	-	-	<1	-	-	<1
Dyspnea	<1	1 to 10	6	-	~10	3	2 to 5	-
Hypersensitivity pneumonitis	✔	-	-	-	-	-	-	-
Pleuritis	<1	-	-	-	-	-	-	-
Pneumonitis	✔	-	-	-	<1	-	-	<1
Pulmonary alveolar hemorrhage	<1	-	-	-	-	-	-	-
Pulmonary edema	<1	-	-	-	-	-	-	-
Pulmonary fibrosis	✔	-	-	-	-	<1	-	-
Pulmonary inflammation	✔	-	-	-	-	-	-	-
Pulmonary mass	<1	-	-	-	-	-	-	-
Pulmonary toxicity	2 to 17	-	-	-	-	-	-	-
Respiratory failure	<1	<1	-	-	-	-	-	<1

Adverse Events	Amiodarone	Disopyramide	Dofetilide	Dronedarone	Flecainide	Mexiletine	Propafenone	Quinidine
Respiratory tract infection	-	-	7	-	-	-	-	-
Wheezing	<1	-	-	-	-	-	-	1 to 10
Other								
Abnormal smell	1 to 10	-	-	-	-	-	-	-
Anaphylactic shock	<1	-	-	-	-	-	-	-
Blood urea nitrogen increased	-	<1	-	-	-	-	-	-
Bone marrow granuloma	<1	-	-	-	-	-	-	-
Cholestatic jaundice	-	<1	-	-	-	-	-	-
Cinchonism	-	-	-	-	-	-	-	<1
Diaphoresis	-	-	-	-	-	-	1	-
Flu syndrome	-	-	4	-	-	-	-	-
Hearing impairment	-	-	-	-	-	-	-	<1
Hypoxia	<1	-	-	-	-	-	-	-
Increased bleeding time	-	-	-	-	-	-	<1	-
Increased creatine phosphokinase	-	-	-	-	-	-	-	<1
Lymphadenopathy	-	-	-	-	-	-	-	<1
Myelofibrosis	-	-	-	-	-	<1	-	-
Pancreatitis	<1	-	-	-	-	<1	-	-
Pseudotumor cerebri	<1	-	-	-	-	-	-	-
Sicca syndrome	-	-	-	-	-	-	-	<1
Syndrome of inappropriate antidiuretic hormone secretion	<1	-	-	-	-	-	<1	-
Thyroid cancer/nodules	<1	-	-	-	-	-	-	-
Thyrotoxicosis	<1	-	-	-	-	-	-	-
Tinnitus	-	-	-	-	1 to 3	2 to 3	<1	1 to 10
Vascular collapse	-	-	-	-	-	-	-	<1
Vasculitis	-	-	-	-	-	-	-	<1

✔ Percent not specified.
- Event not reported.

Table 7. Boxed Warning for Amiodarone[19]

WARNING
Life-threatening arrhythmias: Amiodarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity. **Potentially fatal toxicities:** Amiodarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10% to 17% in some series of patients with ventricular arrhythmias given doses of approximately 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal approximately 10% of the time. Liver injury is common with amiodarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, amiodarone can exacerbate the arrhythmia (e.g., by making the arrhythmia less well tolerated or more difficult to reverse). This has occurred in 2% to 5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2% to 5%. In most cases, all of these events should be manageable in the proper clinical setting. Although the frequency of such proarrhythmic events does not appear greater with amiodarone than with many other agents used in this population, the effects are prolonged when they occur. **High-risk patients:** Even in patients at high risk of arrhythmic death in whom the toxicity of amiodarone is an acceptable risk, amiodarone poses major management problems that could be life-threatening in a population at risk of sudden death; therefore, make every effort to utilize alternative agents first. The difficulty of using amiodarone effectively and safely poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of amiodarone is given, and a response generally requires at least one week, usually two weeks or more. Because absorption and elimination are variable, maintenance dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 patients required dose reduction and 18 required at least temporary discontinuation because of adverse reactions, and several series have reported 15% to 20% overall frequencies of discontinuation because of adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when amiodarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when amiodarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

Table 8. Boxed Warning for Disopyramide[19]

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an myocardial infarction more than six days but less than two years previously, an excessive mortality or nonfatal cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide compared to that seen in patients assigned to carefully matched placebo-treated groups (3%). The average duration of treatment with encainide or flecainide in this study was 10 months. The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain. Considering the known proarrhythmic properties of disopyramide and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, the use of disopyramide as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Table 9. Boxed Warning for Dofetilide[19]

WARNING
To minimize the risk of induced arrhythmia, patients initiated or re-initiated on dofetilide should be placed for a minimum of 3 days in a facility that can provide calculations of creatinine clearance, continuous

WARNING
electrocardiographic monitoring, and cardiac resuscitation. For detailed instructions regarding dose selection, see Administration and Dosage. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.

Table 10. Boxed Warning for Dronedarone[19]

WARNING
Increased risk of death, stroke, and heart failure: Dronedarone is contraindicated in patients with symptomatic heart failure with recent decompensation requiring hospitalization or New York Heart Association class IV heart failure. Dronedarone doubles the risk of death in these patients. Dronedarone is contraindicated in patients in atrial fibrillation (AF) who will not or cannot be cardioverted into normal sinus rhythm. In patients with permanent AF, dronedarone doubles the risk of death, stroke, and hospitalization for heart failure.

Table 11. Boxed Warning for Flecainide[19]

WARNING
Mortality: Flecainide was included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously. An excessive mortality or non-fatal cardiac arrest rate was seen in patients treated with flecainide compared to that seen in patients assigned to a carefully matched placebo-treated group. This rate was 5.1% for flecainide and 2.3% for the matched placebo. The average duration of treatment with flecainide in this study was 10 months. The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) is uncertain, but at present, it is prudent to consider the risks of Class Ic agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs. **Ventricular proarrhythmic effects in patients with atrial fibrillation/flutter:** A review of the world literature revealed reports of 568 patients treated with oral flecainide for paroxysmal atrial fibrillation/flutter. Ventricular tachycardia was experienced in 0.4% of these patients. Of 19 patients in the literature with chronic atrial fibrillation, 10.5% experienced ventricular tachycardia (VT) or ventricular fibrillation (VF). Flecainide is not recommended for use in patients with CAF. Case reports of ventricular proarrhythmic effects in patients treated with flecainide for atrial fibrillation/flutter have included increased premature ventricular contractions, VT, VF, and death. As with other Class I agents, patients treated with flecainide for atrial flutter have been reported with 1:1 atrioventricular conduction due to slowing the atrial rate. A paradoxical increase in the ventricular rate also may occur in patients with atrial fibrillation who receive flecainide. Concomitant negative chronotropic therapy such as digoxin or β-blockers may lower the risk of this complication.

Table 12. Boxed Warning for Propafenone[19]

WARNING
In the National Heart, Lung, and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had an myocardial infarction more than 6 days but less than 2 years previously, an increased rate of death or reversed cardiac arrest rate (7.7%) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared to that seen in patients assigned to placebo (3%). The average duration of treatment with encainide or flecainide in this study was 10 months. The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) or

WARNING

other antiarrhythmic drugs is uncertain, but at present, it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be avoided in patients with nonlife-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening symptoms or signs.

VII. Dosing and Administration

The usual dosing regimens for the antiarrhythmic agents are listed in Table 13.

Table 13. Usual Dosing Regimens for the Antiarrhythmic Agents[11-19]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amiodarone	Ventricular arrhythmias: Injection (Nextrone®): initial, 1,000 mg IV over 24 hours; maintenance, 720 mg IV per 24 hours; in the event of breakthrough episodes of ventricular fibrillation or hemodynamically unstable ventricular tachycardia, use 150 mg IV supplemental infusions Injection, tablet: initial, loading dose of 800 to 1,600 mg/day for one to three weeks, followed by 600 to 800 mg/day for one month; maintenance, 400 to 600 mg/day	Safety and efficacy in pediatrics have not been established.	Tablet: 100 mg 200 mg 400 mg Injection: 50 mg/mL 150 mg/mL
Disopyramide	Ventricular arrhythmias: Capsule, extended-release capsule: 400 to 800 mg/day administered in divided doses Capsule (when rapid control of ventricular arrhythmia is essential): initial, loading dose of 200 or 300 mg; maintenance, 400 to 800 mg/day administered in divided doses	Safety and efficacy in pediatrics have not been established.	Capsule: 100 mg 150 mg Extended-release capsule: 100 mg 150 mg
Dofetilide	Atrial arrhythmias: Capsule: 500 µg twice daily; dosage must be individualized according to calculated creatinine clearance and QTc	Safety and efficacy in pediatrics have not been established.	Capsule: 125 µg 250 µg 500 µg
Dronedarone	Atrial arrhythmias: 400 mg twice daily	Safety and efficacy in pediatrics have not been established.	Tablet: 400 mg
Flecainide	Atrial arrhythmias: Tablet (prevention of paroxysmal atrial fibrillation/flutter): initial, 50	Safety and efficacy in pediatrics have not been established.	Tablet: 50 mg 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg every 12 hours; maintenance, doses may be increased in increments of 50 mg twice daily every four days until efficacy is achieved <u>Ventricular arrhythmias:</u> Tablet (prevention of paroxysmal supraventricular tachycardias): initial, 50 mg every 12 hours; maintenance, doses may be increased in increments of 50 mg twice daily every four days until efficacy is achieved; maximum, 300 mg/day Tablet (prevention of ventricular arrhythmias): initial, 100 mg every 12 hours; maintenance, up to 150 mg every 12 hours; maximum, 400 mg/day		
Mexiletine	<u>Ventricular arrhythmias:</u> Capsule: initial, loading dose of 400 mg, followed by 200 mg every eight hours OR 200 mg every eight hours; maintenance, 200 to 300 mg given every eight hours; maximum, 1,200 mg/day	Safety and efficacy in pediatrics have not been established.	Capsule: 150 mg 200 mg 250 mg
Propafenone	<u>Atrial arrhythmias:</u> Extended-release capsule: initial, 225 mg every 12 hours; maintenance, 325 to 425 mg every 12 hours Tablet: initial, 150 mg every eight hour; maintenance, 225 to 300 mg every eight hours; maximum, usefulness and safety of doses >900 mg/day have not been established <u>Ventricular arrhythmias:</u> Tablet: initial, 150 mg every eight hour; maintenance, 225 to 300 mg every eight hours; maximum, usefulness and safety of doses >900 mg/day have not been established	Safety and efficacy in pediatrics have not been established.	Extended-release capsule: 225 mg 325 mg 425 mg Tablet: 150 mg 225 mg 300 mg
Quinidine	<u>Atrial arrhythmias:</u> Injection: <5 to 10 mg/kg IV as a total dose; if conversion to sinus rhythm has not been achieved after infusion of 10	Safety and efficacy for the treatment of atrial and ventricular arrhythmias in pediatrics have not been established.	Extended-release tablet: 300 mg (quinidine sulfate) 324 mg (quinidine

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg/kg, then the infusion should be discontinued, and other means of conversion should be considered <u>Ventricular arrhythmias:</u> Injection: <5 to 10 mg/kg IV as a total dose; if conversion to sinus rhythm has not been achieved after infusion of 10 mg/kg, then the infusion should be discontinued, and other means of conversion should be considered <u>*P falciparum* malaria:</u> Injection: initial, loading dose of 15 mg/kg; maintenance, 7.5 mg/kg infused over four hours every eight hours for seven days OR initial, loading dose of 6.25 mg/kg; maintenance, 12.5 µg/kg/min Tablet: maintenance, 300 mg every eight hours for seven days OR maintenance, provide approximately as much daily quinine base as the patient had been receiving quinidine base	<u>*P falciparum* malaria:</u> Injection: initial, loading dose of 6.25 mg/kg; maintenance, 12.5 µg/kg/min Tablet: maintenance, 300 mg every eight hours for seven days OR maintenance, provide approximately as much daily quinine base as the patient had been receiving quinidine base	gluconate) Injection (quinidine gluconate): 80 mg/mL Tablet (quinidine sulfate): 200 mg 300 mg

IV=intravenous.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antiarrhythmic agents are summarized in Table 14.

Table 14. Comparative Clinical Trials with the Antiarrhythmic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cairns et al.[21] (1997) CAMIAT Amiodarone loading dose of 10 mg/kg in 2 divided doses daily for 2 weeks, followed by 300 to 400 mg/day for 3 to 5 months, then 200 to 300 mg/day for 4 months, and finally 200 mg/day for 5 to 7 days per week for 16 months vs placebo	DB, MC, PC, RCT Patients >19 years who had an acute MI within the previous 6 to 45 days, and the development of new 40 ms Q-waves in ≥2 adjacent ECG leads or the development of a dominant R-wave in V1, 24 hour ambulatory ECG monitoring that recorded a mean of ≥10 VDPs per hour (≥18 hours of monitoring required), or at ≥1 run of VT	N=1,202 2 years	Primary: RVF or AD Secondary: AD, cardiac death, all-cause mortality	Primary: Twenty five patients receiving amiodarone compared to 39 patients receiving placebo experienced an RVF or AD (RR reduction, 38.2; 95% CI, -2.1 to 62.6; P=0.029). Secondary: Twenty four patients receiving amiodarone compared to 33 patients receiving placebo experienced an AD (RR reduction, 29.3; 95% CI, -19.6 to 58.2; P=0.097). Cardiac mortality was not significant between amiodarone and the placebo groups (44 vs 55 patients respectively; RR reduction 22.0; 95% CI, -15.9 to 47.6; P=0.108). All-cause mortality was not significant between the amiodarone and placebo groups (57 vs 68 patients respectively; RR reduction, 18.3; 95% CI, -16.1 to 42.6; P=0.129).
Julian et al.[22] (1997) EMIAT Amiodarone 800 mg daily for 2 weeks, followed by 400 mg/day for 14 weeks, followed by 200	DB, MC, PC, RCT Patients 18 to 75 years who survived ≥5 days post documentation of an MI, LVEF of ≤40% on MUGA done 5 to 21 days after admission to the	N=1,486 2 years	Primary: All-cause mortality Secondary: Cardiac mortality, AD and AD plus resuscitated cardiac arrest	Primary: There was not a significant difference in all-cause mortality between the amiodarone and placebo groups (102 vs 103 patients in group; risk ratio, 0.99; 95% CI, 0.76 to 1.31; P=0.96). Secondary: There was not a significant difference in total cardiac mortality between the amiodarone and placebo groups (89 vs 85 patients; risk ratio, 0.94; 95% CI, 0.70 to 1.26; P=0.67).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day until the end of the trial vs placebo	coronary-care unit			The amiodarone group had a lower number of patients who experienced an AD compared to the patients in the placebo group (50 vs 33 patients; risk ratio, 0.65; 95% CI, 0.42 to 1.00; P=0.05). The amiodarone group had a lower number of patients who experienced an AD and resuscitated cardiac arrest compared to the patients in the placebo group (61 vs 42 patients; risk ratio, 0.68; 95% CI, 0.46 to 1.00; P=0.05).
Deedwania et al.[23] (1998) CHF-STAT Amiodarone 800 mg QD for 2 weeks, followed by 400 mg QD for 50 weeks, followed by 300 mg QD vs placebo	DB, MC, PC Patients with history of heart failure (≥3 months), NYHA class II, III, or IV, LVEF ≤40%, evidence of dilated cardiomyopathy, dyspnea on exertion or history of paroxysmal nocturnal dyspnea, and frequent ventricular premature beats on 24-hour Holter monitoring	N=667 4.5 years	Primary: Rate control vs conversion to sinus rhythm in atrial fibrillation patients Secondary: Occurrence of new atrial fibrillation	Primary: From time points at two weeks and beyond, the ventricular rates of those patients in the amiodarone treatment group were significantly lower than those in the placebo group (P=0.001 at week 2, and P=0.006 at months 6 and 12). Of the patients that had AF at baseline, 16 patients in the amiodarone group compared to four patients in the placebo group, spontaneously converted to sinus rhythm (P=0.002). Secondary: Eleven patients in the amiodarone group compared 22 patients in the placebo group experienced new-onset AF (P=0.005). Patients in the amiodarone group who spontaneously converted to sinus rhythm and maintained it during the follow-up period had significantly lower mortality compared to those who remained in AF (P=0.04).
Kochiadakis et al.[24] (2004) Amiodarone 15 mg/kg QD for 7 days, followed by 10 mg/kg QD for 7 days, then tapered dose over 7 to 12 days to maintenance levels	RCT, SB Patients >18 years of age, ECG documentation of AF, symptoms such as light-headedness, palpitation, chest pain, and dyspnea in association with AF; successful chemical or	N=146 3 years	Primary: Time to adverse events (relapse to AF or intolerable side effects), whichever occurred first Secondary: Maintenance of AF free time	Primary: There was not a significant difference between the amiodarone and propafenone groups for the suppression of recurrent symptomatic AF or in side effects (P=0.44). Secondary: Amiodarone and propafenone were equally effective in maintaining sinus rhythm without side effects included (P=0.058).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
over 7 to 12 days to a maintenance dose of 200 mg QD vs propafenone 150 to 300 mg followed by a maintenance dose of 150 mg TID	electrical cardioversion to sinus rhythm in the patients with persistent AF			
Gulizia et al.[25] (2008) PITAGORA Amiodarone 600 mg/day for 10 days, followed by 400 mg/day for 10 days, followed by 200 mg/day thereafter vs class Ic antiarrhythmic drugs (flecainide 200 mg/day, propafenone 450 to 600 mg/day)	MC, RCT, SB Patients with SND, ≥3 episodes of symptomatic AT in the 12 months before enrollment, and ≥1 AT episode documented by ECG or Holter recording	N=176 21 months	Primary: Composite of death, permanent AT, cardiovascular hospitalization, atrial cardioversion, or interruption of the randomly assigned antiarrhythmic drug regimen Secondary: AT-related composite end point (permanent AT, hospitalizations due to AT recurrences, atrial cardioversions, and assigned antiarrhythmic drug discontinuation	Primary: The primary end point occurred in 30.7% of patients in the class Ic group and 40.0% of patients in the amiodarone group (P=0.24). Secondary: Death occurred in 2.7% of patients receiving class Ic agents and 8.6% of patients receiving amiodarone (P=0.16). Twelve patients receiving amiodarone were hospitalized for cardiovascular causes compared to nine patients receiving class Ic drugs. Ischemic stroke occurred in two amiodarone patients. After one year, the AT-related composite end point was 22% for amiodarone and 22% for class Ic agents (23% for propafenone and 21% for flecainide; P=0.1). After one year, freedom from AT episodes at >10 minutes, one day, and seven days was 40, 73, and 91%, respectively, for amiodarone and 28, 78, and 86%, respectively for class Ic agents. The mean number of AT-related symptoms at the baseline was 2.0 in the amiodarone group and 2.2 in class Ic group. At the first follow-up visit, the mean number of AT-related symptoms decreased to 0.7 and 1.1, respectively (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			because of lack of efficacy), AT-related symptoms, QOL	QOL scores improved from baseline values of 52 in the amiodarone group and 54 in the class Ic group to 67 and 67, respectively, at the first follow-up visit (P<0.01). There was no significant difference between the treatment groups with regards to AT-related symptoms and QOL scores.
Kojuri et al.[26] (2009) Amiodarone 200 mg BID from 7 days before surgery to 5 days post surgery vs propranolol 20 mg BID from 7 days before surgery to 5 days post surgery vs amiodarone 200 mg BID plus propranolol 20 mg BID from 7 days before surgery to 5 days post surgery	DB, PRO, RCT Patients who underwent elective CABG	N=240 12 days	Primary: Percentage of patients who developed post-CABG AF Secondary: Not reported	Primary: Post-CABG AF developed in 22 patients (9.2%), of whom 13 (16.3%) received propranolol, five (6.3%) received amiodarone and four (5.0%) received combination therapy. The difference in AF between propranolol and amiodarone monotherapy was significant (P=0.02), but not between either monotherapy with combination therapy (P=0.6 and P=0.76). The duration of AF episodes was <24 hours in four patients (80%) receiving amiodarone, nine patients (69.2%) receiving propranolol and four patients (100%) receiving combination therapy (P values not reported). Secondary: Not reported
Lee et al.[27] (2008) Amiodarone vs sotalol	RETRO Patients with AF and/or CHF (NYHA class ≥III) and an implantable cardioverter defibrillator	N=55 2.6±2.0 years	Primary: Cumulative rates of inappropriate shocks Secondary: Not reported	Primary: Amiodarone demonstrated a significantly lower rate of inappropriate shock compared to the beta-blockers (27.3 vs 70.6% at four years; P=0.003). This demonstrated an 83% reduction compared to the beta-blockers (HR, 0.17; 95% CI, 0.05 to 0.64; P=0.008). There was not a significant difference in rates of inappropriate shocks observed between the amiodarone and sotalol groups (27.3 vs 54.3% at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs beta-blockers (agents not specified) Doses of the agents were not specified.				four years; P=0.29). There was not a significant difference in rates of inappropriate shocks observed between the sotalol and beta-blocker groups (54.3 vs 70.6% at four years; P=0.16). Secondary: Not reported
Connolly et al.[28] (2006) OPTIC Beta-blocker (bisoprolol, carvedilol or metoprolol) vs sotalol 240 mg/day in 2 to 3 divided doses vs amiodarone 200 mg/day plus β-blocker (bisoprolol, carvedilol or metoprolol) Amiodarone was loaded at 400 mg BID for 2 weeks,	DB, MC, RCT Patients who received an implantable cardioverter defibrillator within 21 days of randomization, had sustained ventricular tachycardia, ventricular fibrillation or cardiac arrest (not ≤72 hours of acute MI), LVEF ≤40%, inducible ventricular tachycardia or ventricular fibrillation by programmed ventricular stimulation with LVEF ≤40% or unexplained	N=412 12 months	Primary: Implantable cardioverter defibrillator shock for any reason Secondary: Not reported	Primary: Shocks occurred in 41 patients (38.5%) in the beta-blocker group, 26 (24.3%) patients in the sotalol group, and 12 (10.3%) patients in the amiodarone plus beta-blocker group. A reduction in the risk of shock was observed with use of amiodarone plus beta-blocker or sotalol vs beta-blocker alone (HR, 0.44; 95% CI, 0.28 to 0.68; P<0.001). The amiodarone plus beta-blocker group significantly reduced the risk of shock compared to the beta-blocker alone group (HR, 0.27; 95% CI, 0.14 to 0.52; P<0.001) and the sotalol group (HR, 0.43; 95% CI, 0.22 to 0.85; P=0.02). The sotalol group did not significantly reduce the risk of shock compared to the beta-blocker alone group (HR, 0.61; 95% CI, 0.37 to 1.01; P=0.055). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 400 mg/day for 4 weeks, and then 200 mg/day until then end of the study	syncope with ventricular tachycardia or ventricular fibrillation, inducible by programmed stimulation			
Torp-Pederson et al.[29] (1999) Dofetilide 250 µg QD to 500 µg BID vs placebo	DB, MC, PC, RCT Patients ≥18 years hospitalized with new or worsening CHF and who had ≥1 episode of shortness of breath on minimal exertion or at rest or paroxysmal nocturnal dyspnea	N=1,518 1 year	Primary: Death from any cause Secondary: Death from cardiac causes, death from arrhythmia, death from cardiac causes or successful resuscitation after cardiac arrest, arrhythmias requiring treatment, worsening CHF and MI, and in patients with baseline AF, incidence of conversion to and maintenance of sinus rhythm	Primary: Death did not differ significantly between dofetilide treatment group and placebo (311 [41%] vs 317 [42%] respectively; HR, 0.95; 95% CI, 0.81 to 1.11; P=0.54). Secondary: There was not a significant difference in death from cardiac causes between dofetilide treatment group and placebo (33 vs 33%, respectively). There was not a significant difference in death from arrhythmias between dofetilide treatment group and placebo (20 vs 20%, respectively). Fewer hospitalizations due to worsening heart failure were experienced in the dofetilide group compared to placebo (30 vs 38%, respectively). There was a significant greater number of patients with AF at baseline who converted to sinus rhythm in the dofetilide compared to those patients with AF at baseline in the placebo group. At one month: 12 vs 2%, respectively (P<0.001) and at 12 months: 44 vs 13%, respectively (P<0.001). After cardioversion, more patients with baseline AF in the dofetilide group maintained sinus rhythm compared to those patients in the placebo group (HR, 0.35; 95% CI, 0.22 to 0.57; P<0.001).
Singh et al.[30] (2007) EURIDIS and ADONIS	DB, MC, RCT Patients ≥21 years of age with ≥1 episode of AF in the	N=1,237 1 year	Primary: Time from randomization to the first documented	Primary: In EURIDIS, the median times from randomization to a documented recurrence of AF were 96 days in the dronedarone group and 41 days in the placebo group. At 12 months, 67.1% of patients in the dronedarone group and 77.5% of patients in the placebo group had had a recurrence of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dronedarone 400 mg BID vs placebo	preceding 3 months who were in sinus rhythm for ≥1 hour before randomization		recurrence of AF Secondary: Symptoms related to AF during recordings of 12-lead electro-cardiography or transtelephonic monitoring and the mean ventricular rate during the first recurrence	atrial fibrillation (HR, 0.78; 95% CI, 0.64 to 0.96; P=0.01). In ADONIS, the median times from randomization to a documented recurrence of AF were 158 days in the dronedarone group and 59 days in the placebo group. At 12 months, 61.1% of patients in the dronedarone group and 72.8% of patients in the placebo group had had a recurrence of AF (HR, 0.73; 95% CI, 0.59 to 0.89; P=0.002). In the combined analysis, the median times to a documented recurrence of AF were 116 days in the dronedarone group and 53 days in the placebo group. At 12 months, the rates of recurrence were 64.1% in the dronedarone group and 75.2% in the placebo group (HR, 0.75; 95% CI, 0.65 to 0.87; P<0.001). Secondary: In EURIDIS, 37.1% of patients in the dronedarone group and 47.5% of those in the placebo group had symptomatic recurrences of AF (P=0.006). In ADONIS, symptomatic recurrences occurred in 38.3% of patients in the dronedarone group and 44.5% of those in the placebo group (P=0.02). In the combined analysis, the corresponding numbers were 37.7 and 46.0% (P<0.001). In EURIDIS, the mean ventricular rate during the first adjudicated recurrence was 102.3beats per minute in the dronedarone group and 117.5 beats per minute in the placebo group (P<0.001). In ADONIS, the mean ventricular rate during the first adjudicated recurrence was 104.6 beats per minute in the dronedarone group and 116.6 beats per minute in the placebo group (P<0.001). In EURIDIS, 21.2% of patients in the dronedarone group were hospitalized or died at 12 months compared to 32.0% of those in the placebo group (HR, 0.66; 95% CI, 0.47 to 0.93; P=0.02). In ADONIS, 24.5% of patients in the dronedarone group were hospitalized or died compared to 29.8% of those in the placebo group (HR, 0.80; 95% CI, 0.56 to 1.14; P=0.22). In the combined analysis, the corresponding numbers were 22.8 and 30.9% (HR, 0.73; 95% CI, 0.57 to 0.93; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a higher incidence of elevated serum creatinine levels in the dronedarone group than in the placebo group (2.4 vs 0.2%, P=0.004). Ventricular arrhythmias occurred infrequently in both groups and no episodes of torsades de pointes were reported.
Hohnloser et al.[31] (2009) ATHENA Dronedarone 400 mg BID vs placebo	DB, MC, PC, RCT Patients with paroxysmal or persistent AF or atrial flutter with ≥1 of the following risk factors: ≥70 years of age, arterial hypertension (treated with ≥2 antihypertensive drugs), diabetes mellitus, previous stroke, TIA, or systemic embolism, left atrial diameter ≥50 mm, and LVEF ≤40%	N=4,628 21 months	Primary: First hospitalization due to cardiovascular events or death Secondary: Death from any cause, death from cardiovascular causes, hospitalization due to cardiovascular events	Primary: In the dronedarone group, 31.9% of patients experienced the primary outcome compared to 39.4% of patients in the placebo group (HR, 0.76; 95% CI, 0.69 to 0.84; P<0.001). Secondary: Death from any cause occurred in 5.0% of patients in the dronedarone group and 6.0% of patients in the placebo group (HR, 0.84; 95% CI, 0.66 to 1.08; P=0.18). Cardiovascular death occurred in 2.7% of patients in the dronedarone group and 3.9% of patients in the placebo group (HR, 0.71; 95% CI, 0.51 to 0.98; P=0.03). In the dronedarone group, 29.3% of patients had a first hospitalization due to cardiovascular events compared to 36.9% of patients in the placebo group (HR, 0.74; 95% CI, 0.67 to 0.82; P<0.001). Bradycardia, QT-interval prolongation, diarrhea, nausea, rash, and an increase in the serum creatinine level were significantly more common in the dronedarone group than in the placebo group. Pulmonary symptoms, interstitial lung disease, and abnormalities of thyroid function were not significantly more common with dronedarone than with placebo.
Page et al.[32] (2011) ATHENA Dronedarone 400 mg BID vs placebo	Post-hoc analysis of ATHENA Patients with paroxysmal or persistent AF or atrial flutter and additional cardiovascular risk factors, and a 12-	N=3,473 (patients in sinus rhythm at baseline) 21 months	Primary: Time to first AF or atrial flutter recurrence, incidence of electrical cardioversion, likelihood of permanent AF and atrial flutter	Primary: The median time to first AF or atrial flutter recurrence of patients in sinus rhythm at baseline was 498 and 737 days with placebo and dronedarone (HR, 0.749; 95% CI, 0.681 to 0.824; P<0.001). At the time of first AF and atrial flutter recurrence, the mean heart rates were 85.3 and 95.5 bpm with dronedarone and placebo, respectively (P<0.001). Three hundred and thirty nine patients (15%) receiving dronedarone had at least one electrical cardioversion compared to 481 (21%) patients receiving placebo (HR, 0.684; 95% CI, 0.596 to 0.786; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Randomization was stratified according to sinus rhythm status at baseline	lead ECG <6 months before randomization available showing AF or atrial flutter, and a second 12-lead ECG within the same time period had to show sinus rhythm		Secondary: Not reported	The likelihood of permanent AF and atrial flutter was lower with dronedarone (7.6 vs 12.8% of patients; HR, 0.749; 95% CI, 0.681 to 0.824; P<0.001). Secondary: Not reported
Torp-Pedersen et al.[33] (2011) ATHENA Dronedarone 400 mg BID vs placebo	Post-hoc analysis of ATHENA Patients with paroxysmal or persistent AF or atrial flutter with ≥1 of the following risk factors: ≥70 years of age, arterial hypertension (treated with ≥2 antihypertensive drugs), diabetes mellitus, previous stroke, TIA, or systemic embolism, left atrial diameter ≥50 mm, and LVEF ≤40%	N=4,628 21 months	Primary: Number of first hospitalizations per treatment group, number of hospitalizations after first AF/atrial flutter recurrence, number of all hospitalizations, duration of hospital stay, hospitalization burden over time Secondary: Not reported	Primary: Overall, the number of first cardiovascular hospitalizations was significantly decreased with dronedarone compared to placebo (675 vs 859 patients; HR, 0.74; 95% CI, 0.67 to 0.82; P<0.001). There was no difference between the number of first non-cardiovascular hospitalizations between the two treatments (516 vs 533; P=0.77). Among the patients experiencing at least one AF-related hospitalization during the trial, 50% remained in the hospital for at least four nights and 25% for at least eight nights. The total number of hospitalizations for AF was reduced from 829 with placebo to 514 with dronedarone (HR, 0.626; 95% CI, 0.546 to 0.719; P<0.001) and the number of days in hospital from 4,637 to 3,132, respectively (P<0.001). Dronedarone significantly reduced total hospitalizations for acute coronary syndrome (73 vs 113; P=0.0105) and the number of hospitalization days (816 vs 1,188 days; P=0.04). Dronedarone significantly reduced the time between the first AF/atrial flutter recurrence and cardiovascular hospitalization/death (HR, 0.771; 95% CI, 0.643 to 0.925; P=0.0048). Hospitalization burden was significantly reduced across all levels of care (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Duray et al.[34] (2011) ATHENA/ EURIDIS/ ADONIS Dronedarone 400 mg BID vs placebo	Pooled post-hoc analysis of ATHENA/ EURIDIS/ADONIS trials Individual patients with lone AF who were enrolled in the ATHENA, EURIDIS, and ADONIS trials were entered in a center database	N=432 13.8±7.2 months	Primary: Composite of cardiovascular hospitalizations or death, and the individual components Secondary: Not reported	Primary: The risk of first cardiovascular hospitalizations or all-cause mortality in patients receiving placebo after one year was 25% in the lone AF group compared to 29% in the rest of the population. In patients with lone AF, dronedarone led to a 44% reduction in cardiovascular hospitalizations or all-cause mortality (HR, 0.56; 95% CI, 0.36 to 0.88; P=0.004) and to a 46% reduction in cardiovascular hospitalization (HR, 0.54; 95% CI, 0.34 to 0.87; P=0.004) compared to placebo. There was no significant difference between dronedarone and placebo with regards to all-cause mortality (HR, 1.02; 95% CI, 0.31 to 3.34; P=0.885). Secondary: Not reported
Kober et al.[35] (2008) ANDROMEDA Dronedarone 400 mg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age who were hospitalized with new or worsening heart failure and who had ≥1 episode of shortness of breath on minimal exertion (NYHA functional class III or IV) or paroxysmal nocturnal dyspnea within the month before screening	N=627 An average of 62.1 days and a median follow-up of 2 months	Primary: Composite of death from any cause or hospitalization for worsening heart failure Secondary: Death from all causes, hospitalization for cardiovascular causes, hospitalization for worsening heart failure, occurrence of AF/atrial flutter, death from arrhythmia, or sudden death	The study terminated prematurely due to increased death in the active treatment group. During a median follow-up of two months, 25 (8.1%) patients in the dronedarone group and 12 (3.8%) patients in the placebo group died (HR, 2.13; 95% CI, 1.07 to 4.25; P=0.03). After an additional six months without study treatment, 42 (13.5%) patients in the dronedarone group and 39 (12.3%) patients in the placebo group died (HR, 1.13; 95% CI, 0.73 to 1.71; P=0.60). Subgroup analysis of the study population, after adjustment for risk factors, showed that the most powerful predictor of death was treatment with dronedarone (HR, 2.19; 95% CI, 1.06 to 4.52; P=0.03). Primary: The primary composite endpoint was not significantly different between groups (17.1% [53 events] for dronedarone vs 12.6% [40 events] for placebo; HR, 1.38; 95% CI, 0.92 to 2.09; P=0.12). After an additional six months of follow-up after treatment discontinuation, 74 patients (23.9%) and 72 patients (22.7%) in the dronedarone and placebo groups, respectively, had reached the primary composite endpoint (HR, 1.09; 95% CI, 0.79 to 1.51; P=0.60).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: First hospitalization for cardiovascular cause was higher in the dronedarone group than the placebo group (71 vs 50; P=0.02) with the main reason being worsening heart failure (49.3% for the dronedarone group and 60.0% for the placebo group). Other reasons for hospitalization for cardiovascular causes included MI (18.3 and 16.0%; in the dronedarone and placebo groups, respectively), ventricular arrhythmia (4.2 and 4.0%), supraventricular arrhythmia (5.6 and 2.0%), stroke (5.6 and 6.0%), other cardiovascular events (12.7 and 8.0%), and presumed cardiovascular events (4.2 and 4.0%). At one month, there was no significant difference between the two groups in the percentage of patients who had AF (21.4% for the dronedarone group vs 24.8% for the placebo group; P value not reported). Ten (3.2%) patients and six (1.9%) patients in the dronedarone and placebo groups died from arrhythmia or sudden death during the double-blind, randomized study period. This difference was not significantly different (P value not reported).
Touboul et al.[36] (2003) DAFNE Dronedarone 400 mg BID vs dronedarone 600 mg BID vs dronedarone 800 mg BID vs	DB, PC, RCT Patients 21 to 85 years of age with persistent AF for whom cardioversion and antiarrhythmic treatment was warranted	N=270 6 months	Primary: Time to first documented AF recurrence Secondary: Spontaneous conversion of AF following randomization, heart rate in case of AF recurrence, and incidence of side effects	Primary: Only in the 400 mg twice daily arm was the time to AF relapse significantly different from placebo (60.0 vs 5.3 days; RR reduction, 55%; 95% CI, 72 to 28; P=0.001). Secondary: There was a dose-effect relationship to the incidence of spontaneous conversion to sinus rhythm (P=0.0261) with patients in all dronedarone groups (400, 600, and 800 mg) exhibiting spontaneous conversion to sinus rhythm (5.8, 8.2 and 14.8%, respectively, vs 3.1% for the placebo group). Dronedarone appeared to slow ventricular rate during AF recurrence in a dose-dependent manner. The rate was reduced by 13.2, 19.2 and 17.8 bpm vs placebo (P=0.0001). Discontinuation rates due to adverse events were 10.8% with dronedarone treated patients (3.9, 7.6 and 22.6%, respectively) vs 0% with placebo treated patients (P value not reported). Most commonly reported effects

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				were gastrointestinal related.
Davy et al.[37] (2008) ERATO Dronedarone 400 mg BID vs placebo	DB, MC, PC, RCT Adult patients ≥21 years with documented, symptomatic permanent AF, for which cardioversion was not considered an option	N=174 6 months	Primary: Change in mean ventricular rate measured by 24-hour Holter recording on day 14 Secondary: Change in mean ventricular rate during submaximal and maximal exercise at day 14, change in maximal exercise duration at day 14, change in mean ventricular rate measured by 24-hour Holter after 4 months, safety and tolerability	Primary: There was a mean reduction in mean 24-hour ventricular rate of 11.0 beat/min in the dronedarone group at day 14 compared to an increase of 0.7 beat/min in the placebo group (P<.0001). Secondary: There was a reduction in mean heart rate of 25.6 beat/min in the dronedarone group compared to 2.2 beat/min in the placebo group during submaximal exercise (P<0.0001). There was a reduction in mean heart rate of 27.4 beat/min in the dronedarone group compared to 2.9 beat/min in the placebo group at maximal exercise (P<0.0001). There was a mean increase in maximal exercise duration of 0.14 and 0.26 minutes in the dronedarone and placebo groups, respectively (P=0.514). The mean change in 24-hour Holter-monitored ventricular heart rate was greater with dronedarone compared to placebo at four months (-10.1 vs -1.3 beat/min, respectively; P<0.001). Dronedarone was well tolerated throughout the study. There were no cases of torsades de pointes or sustained ventricular tachycardia reported in either treatment group. The incidence of treatment-emergent adverse events was higher with dronedarone than placebo. Gastrointestinal disturbances occurred in 20% of patients receiving dronedarone compared to 13.5% of those receiving placebo.
Køber et al.[38] (2008) ANDROMEDA Dronedarone 400 mg BID vs	DB, MC, PC, RCT Patients ≥18 years of age who were hospitalized with new or worsening heart failure and who had	N=627 7 months	Primary: Death from any cause or hospitalization for worsening heart failure Secondary:	Primary: The data and safety monitoring board recommended that the trial be terminated early due to an excess of deaths in the dronedarone group. Death from any cause occurred in 8.1% of patients receiving dronedarone and 3.8% of patients receiving placebo (HR, 2.13; 95% CI, 1.07 to 4.25; P=0.03). The number of deaths that were attributed to arrhythmia or sudden death did not differ significantly between the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	had ≥1 episode of shortness of breath on minimal exertion or at rest (NYHA III or IV), paroxysmal nocturnal dyspnea, or a wall-motion index ≤1.2		Death from all causes, hospitalization for cardiovascular causes, hospitalization for worsening heart failure, occurrence of AF or atria flutter, death from arrhythmia, or sudden death	The primary combined end point of all-cause mortality or hospitalization for worsening heart failure was not different between dronedarone and placebo (17.1 vs 12.6%, respectively; HR, 1.38; 95% CI, 0.92 to 2.09; P=0.12). Secondary: The total number of patients who had a first hospitalization for an acute cardiovascular cause was higher in the dronedarone group than in the placebo group (P=0.02). The main reason for hospitalization for a cardiovascular cause was worsening heart failure (49.3% in the dronedarone group and 60.0% in the placebo group). Other cardiovascular events requiring a first hospitalization in the dronedarone group compared to placebo were myocardial ischemia (18.3 vs 16.0%, respectively), ventricular arrhythmia (4.2 vs 4.0%, respectively), supraventricular arrhythmia (5.6 vs 2.0%, respectively), stroke (5.6 vs 6.0%, respectively), other cardiovascular events (12.7 vs 8.0%, respectively), and presumed cardiovascular events (4.2 vs 4.0%, respectively). There were no significant differences detected between the two groups with regards to serious adverse events, except for increases in the serum creatinine concentration, which were observed more frequently in the dronedarone group than in the placebo group. At the one month visit, 21.4% of the patients in the dronedarone group had AF compared to 24.8% of patients receiving placebo (P value not significant). No cases of torsades de pointes were observed in either group.
Connolly et al.[39] (2011) PALLAS Dronedarone 400 mg BID vs	DB, MC, PC, RCT Patients ≥65 years of age with ≥6 month history of permanent AF or atrial flutter and risk factors for major vascular events	N=3,236 1 year	Primary: Composite of stroke, MI, systemic embolism, or death from cardiovascular causes; composite of unplanned	After enrollment of 3,236 patients the trial was stopped for safety reasons. Primary: The first coprimary endpoint (composite of stroke, MI, systemic embolism, or death from cardiovascular causes) occurred in 43 and 19 patients receiving dronedarone and placebo (HR, 2.29; 95% CI, 1.34 to 3.94; P=0.002). There were 21 and 10 cardiovascular deaths with dronedarone and placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	(coronary artery disease; pervious stroke or TIA; symptomatic heart failure; LVEF ≤40%; peripheral arterial disease; or the combination of age ≥75 years, hypertension, and diabetes)		hospitalization for a cardiovascular cause or death Secondary: Safety	(HR, 2.11; 95% CI, 1.00 to 4.49; P=0.046), including death from arrhythmia in 13 and four patients, respectively (HR, 3.26; 95% CI, 1.06 to 10.0; P=0.03). Stroke occurred in 23 and 10 patients receiving dronedarone and placebo (HR, 2.32; 95% CI, 1.11 to 4.88; P=0.02). Hospitalization for heart failure occurred in 43 and 24 patients receiving dronedarone and placebo (HR, 1.81; 95% CI, 1.10 to 2.99; P=0.02). Secondary: The most common adverse events were diarrhea, asthenic condition, nausea and vomiting, dizziness, dyspnea, and bradycardia. An increase of alanine aminotransferase of more than three times the upper limit of normal range occurred in 1.5 and 0.6% of patients receiving dronedarone and placebo (P=0.013).
Le Huezey et al.[40] (2010) DIONYSOS Dronedarone 400 mg BID vs amiodarone 600 mg/day for 28 days then 200 mg/day thereafter	DB, MC, PG, RCT Patients ≥21 years of age with documented AF for >72 hours, for whom antiarrhythmic drugs and cardioversion were indicated, and who received oral anticoagulation	N=504 6 months	Primary: Composite of time to first AF recurrence or premature study drug discontinuation for intolerance or lack of efficacy, and safety evaluation of occurrence of thyroid, hepatic, pulmonary, neurological, skin, ocular, or gastrointestinal events or premature drug discontinuation following an adverse event	Primary: At 12 months the incidence of the primary composite endpoint was 75.1% in the dronedarone group and 58.8% in the amiodarone group (HR, 1.59; 95% CI, 1.28 to 1.98; P<0.0001). The crude rates of the components of the primary composite endpoints of AF recurrence compared to premature study drug discontinuation was 63.5 vs 10.4% in the dronedarone group and 42.0 vs 13.3% in the amiodarone group. This demonstrates that the primary endpoint was mainly driven by AF recurrence. In the AF recurrence component of the endpoint, AF after electrical cardioversion occurred in 36.5 and 24.3% of patients in the dronedarone and amiodarone groups, respectively (P value not reported). At 12 months the incidence of the primary safety endpoint was 39.3% in the dronedarone group and 44.5% in the amiodarone group (HR, 0.8; 95% CI, 0.60 to 1.07; P=0.129). The difference between the two groups was mainly driven by increased thyroid, neurologic, skin, and ocular events in the amiodarone group. There was a higher incidence of gastrointestinal events, mainly diarrhea in the dronedarone group (9.2%) compared to the amiodarone group (3.1%). A pre-specified endpoint of the main safety event excluding gastrointestinal effects showed a 39% RR reduction in favor of dronedarone (HR, 0.61; 95% CI, 0.44 to 0.84; P=0.002). When

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	the components of the main safety events were analyzed separately, there was a RR reduction of 84.2% (P=0.0006) in the incidence of thyroid events and 87.6% (P=0.0001) in the incidence of neurologic events favoring dronedarone. Secondary: Not reported
Piccini et al.[41] (2009) Dronedarone 400 mg BID vs amiodarone 200 mg QD	MA Patients with AF	N=7,140 13 to 16 months (mean duration)	Primary: Recurrence of AF, all-cause mortality, adverse events Secondary: Not reported	Primary: *Dronedarone vs placebo* For prevention of AF, the effect of dronedarone had an OR of 0.79 (95% CI, 0.33 to 1.87), with a risk difference of -0.040 (95% CI, -0.19 to 0.11) equivalent to 40 fewer events per 1,000 patients treated. For mortality, the OR was 0.85 (95% CI, 0.66 to 1.11), with a risk difference of -0.003 (95% CI, -0.011 to 0.006). For adverse events requiring discontinuation, there was a significant increase over placebo with OR of 1.166 (95% CI, 1.36 to 2.02) and risk difference 0.045 (95% CI, 0.028 to 0.062). *Amiodarone vs placebo* Amiodarone significantly prevented AF, with an OR of 0.12 (95% CI, 0.08 to 0.19) and a risk difference of -0.401 (95% CI, -0.46 to -0.34) equivalent to 401 fewer events per 1,000 patients treated. For mortality, the OR was 1.88 (95% CI, 0.54 to 6.56), with a risk difference of 0.005 (95% CI, -0.016 to 0.026). For adverse events requiring discontinuation, there was a significant increase over placebo with an OR of 11.04 (95% CI, 1.89 to 64.5) and risk difference of 0.128 (95% CI, 0.023 to 0.230). *Dronedarone vs amiodarone* In the indirect MA, amiodarone significantly reduced the risk of recurrent AF compared to dronedarone (OR, 0.16; 95% CI, 0.06 to 0.42), with a risk difference of -0.36 (95% CI, -0.52 to -0.19), which is equivalent to 360 fewer events per 1,000 patients treated. This was consistent with the direct

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				results from DIONYSOS (OR, 0.44; 95% CI, 0.30 to 0.64), with a risk difference of -0.186 (95% CI, -0.266 to -0.1028). There was a mortality trend favoring dronedarone in the indirect MA (amiodarone vs dronedarone OR, 2.20; 95% CI, 0.61 to 7.88; risk difference: 0.008; 95% CI: -0.015 to 0.030). This finding was consistent with the DIONYSOS trial (OR, 2.44; 95% CI, 0.48 to 12.6), risk difference 0.011 (95% CI, -0.010 to 0.033). For adverse effects requiring interruption of therapy, the indirect MA estimate favored dronedarone; amiodarone was associated with an increased odds of study drug termination (OR, 6.65; 95% CI, 1.13 to 39.3) with a risk difference of 0.083 (95% CI, -0.022 to 0.1866). The effect was similar in DIONYSOS (OR, 2.24; 95% CI, 1.13 to 4.43) with a risk difference of 0.057 (95% CI, 0.010 to 0.105). The incidence of thyroid toxicity (4 vs 3%), symptomatic bradyarrhythmias (2.8 vs 1.1%), and hepatotoxicity (3.5 vs 2.5%) leading to treatment discontinuation were comparable between dronedarone and placebo. There were no cases of torsades de pointes in any of the patients administered amiodarone or in the DIONYSOS trial. There was a single case of torsades de pointes in a patient receiving dronedarone in ATHENA. Secondary: Not reported
Kirchhof et al.[42] Flec-SL Flecainide 200 to 300 mg/day for 4 weeks vs flecainide 200 to	Blinded endpoint, MC, OL, PRO, RCT Adults with persistent AF undergoing planned cardioversion	N=635 6 months	Primary: Time to persistent AF or death, QOL Secondary: Safety	Primary: The first analysis performed with the four week follow-up data for 242 patients, and demonstrated that flecainide (short- and long-term treatment combined) was superior to no treatment (control; 28-day Kaplan-Meier survival of 70.2% [95% CI, 63.0 to 77.3] of patients receiving flecainide vs 52.5% [95% CI, 41.4 to 63.6] of patients receiving control; P=0.0160). On the basis of these findings, an additional analysis was conducted to compare short-term and long-term maintenance treatment; enrollment into the control group ended, and sample size was adjusted from 725 to 635. In

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
300 mg/day for 6 months no treatment (control) Patients were randomized to trial medication after successful cardioversion.				the per protocol population, 120 (46%) of 261 patients receiving short-term treatment developed persistent AF (48.4%; 95% CI, 41.9 to 55.0) vs 103 (39%) of 263 receiving long-term treatment (56.4%; 95% CI, 49.1 to 63.6). No deaths occurred. The difference between the two groups receiving flecainide in the mean percentage of patients who did not have persistent AF was 7.9% (95% CI, -1.9 to 17.7); therefore, noninferiority of short-term to long-term treatment could not be shown (P=0.2081). In the intention-to-treat population, the difference between short-term and long-term treatment was 6.3% (95% CI, -2.6 to 15.3; P=0.1073). In a post-hoc analysis of patients who had not reached the primary endpoint in the first month confirmed that long-term treatment was superior to short-term treatment in the prevention of persistent AF or death (difference between Kaplan-Meier estimates 14.3%; 95% CI, 5.1 to 23.6; P=0.0001; HR, 0.31; 95% CI, 0.118 to 0.56; P<0.0001). QOL improved with short-term and long-term flecainide treatment. In the control group, only physical sores of the SF-12 improved, not mental. Number of admissions because of AF, number of medical visits without admission, left ventricular function at six months, and QOL did not differ between short-term and long-term treatment. Secondary: The number of serious adverse events was low with all treatments, and did not vary between treatments. The number did not differ between patients with coronary artery disease and those without the disorder.
Cast Investigators[43,44] (1993 and 1989) CAST I Encainide* 35 to 50 mg TID, flecainide 100 to 150 mg BID or moricizine* 200 to 250 mg TID	MC, OL, PC, RCT Patients 6 days to 2 years post documented MI who had ≥6 VDPs per hour during an ambulatory ECG recording, and a LVEF of ≤55% if recorded 6 to 90	N=2,371 1 year	Primary: Overall survival and free of cardiac arrest or AD Secondary: Not reported	Primary: After one year of therapy 90% of patients in the active treatment group survived compared to 95% of patients in the placebo group (P=0.0006). A higher total mortality rate was seen in the encainide and flecainide groups: 56 patients (7.7%) taking encainide or flecainide compared to 22 patients (3.0%) taking placebo (RR, 2.5; 95% CI, 1.6 to 4.5). After one year of therapy, 93% of patients in the active treatment group were free of cardiac arrest or AD compared to 96% of patients in the placebo group (P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	days after MI, or ≤40% if recorded 90 days to 2 years post-MI			Encainide and flecainide accounted for the excess of deaths from arrhythmia and nonfatal cardiac arrests: 33 patients (4.5%) taking encainide or flecainide compared to nine patients (1.2%) taking placebo (RR, 3.6; 95% CI, 1.7 to 8.5). After a mean follow up of 10 months, due to a significantly higher death rate in the active treatment group (63 patients) compared to the placebo group (26 patients; P=0.000), the flecainide and encainide arms of this trial were stopped early. Also, death or cardiac arrest due to arrhythmia was significantly higher in the active treatment group (43 patients) compared to the placebo group (16 patients; P=0.0004).
Balla et al.[45] (2011) Flecainide 3 mg/kg, single dose vs amiodarone 30 mg/kg, single dose vs propafenone 8.5 mg/kg, single dose vs placebo	PC, PRO, RCT, SB Patients with recent AF	N=160 48 hours	Primary: Conversion rate at 24 hours after the drug intake Secondary: Safety	Primary: The primary endpoint occurred in 87.5, 85, 85, and 17.5% of patients receiving flecainide, amiodarone, propafenone, and placebo (P<0.001 vs placebo for all three comparisons). Conversion rates within three hours after drug intake was greater with propafenone (57.5%) or flecainide (45%) compared to amiodarone (0%) or placebo (10%). Between six and 24 hours, significantly more patients were converted to sinus rhythm with amiodarone compared to flecainide or propafenone. The use of antiarrhythmic drugs was a significant predictor of conversion to sinus rhythm compared to placebo (adjusted OR, 19.53; 95% CI, 3.14 to 121.55; P<0.001). Secondary: There were no significant adverse effects during the follow-up period in the drug arm. Two patients receiving amiodarone had mild diarrhea.
Kosior et al.[46] (2009) Propafenone 600 mg orally, followed by 300	RCT Patients 18 to 85 years of age admitted to the Emergency	N=81 24 hours	Primary: Restoration of sinus rhythm, safety Secondary:	Primary: Within the first 24 hours, sinus rhythm was restored in 90.7% of patients receiving propafenone and in 91.4% of patients receiving digoxin/quinidine. There was no significant difference in the efficacy after 24 hours of follow-up (90.1 vs 91.4%, respectively; P=0.78).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg after 8 hours if sinus rhythm had not been restored by then vs digoxin 1 mg IV, followed by an oral loading of quinidine (400 mg, followed by 200 mg every 2 hours)	Department with symptomatic recent onset AF <48 hours duration, mean ventricular rate >70 beats per minute, and NYHA functional class <II		Not reported	Propafenone was more effective at restoring sinus rhythm than digoxin/quinidine during the first eight hours (83.3 vs 54.3%, respectively; P<0.01). No life-threatening adverse events were reported during the follow-up. There was no difference in mild adverse events with propafenone compared to digoxin/quinidine (37.2 vs 45.7%, respectively; P=0.56). No case of significant heart failure exacerbation was observed. Secondary: Not reported
Wyse et al.[47] (2002) AFFIRM Rhythm control therapy: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm) vs	MC, RCT Patients 65 years and older who had AF that was likely recurrent, AF was likely to cause illness or death, long-term treatment for AF was warranted, no contraindicated to anticoagulation therapy, eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after	N=4,060 3.5 years	Primary: Overall mortality Secondary: Composite death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest	Primary: The difference in mortality between the two groups was not significant (HR, 1.15; 95% CI, 0.99 to 1.34; P=0.08). Secondary: The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest were also similar in the two groups (P=0.33).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rate control therapy: β-blockers, calcium-channel blockers, digoxin, and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm)	randomization			
Van Gelder et al.[48] (2002) RACE Rhythm control therapy: electrical cardioversion, then sotalol 160 to 320 mg (based on weight and renal function); if recurrence within 6 months, repeat electrical cardioversion, then flecainide 200 to 300 mg QD or propafenone 450 to 900 mg QD; if recurrence again, electrical cardioversion repeated along with amiodarone 600 mg QD for 4	MC, RCT Patients with recurrent persistent AF or atrial flutter, who have undergone one electrical cardioversion during the previous 2 years, with a maximum of 2	N=522 2 years	Primary: Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse effects of antiarrhythmic drugs Secondary: Not reported	Primary: The composite end point occurred in 44 (17.2%) patients in rate-control group and in 60 (22.6%) patients in the rhythm-control group (absolute difference of -5.4; 90% CI, -11.0 to 0.4). Death from cardiovascular causes occurred in 18 (7.0%) patients in rate-control group and in 18 (6.8%) patients in the rhythm-control group (absolute difference of 0.2; 90% CI, -3.4 to 3.9). Heart failure occurred in nine (3.5%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of -1.0; 90% CI, -3.8 to 1.8). Thromboembolic complications occurred in 14 (5.5%) patients in rate-control group and in 21 (7.9%) patients in the rhythm-control group (absolute difference of -2.4; 90% CI, -6.0 to 1.2). Bleeding occurred in 12 (4.7%) patients in rate-control group and in nine (3.4%) patients in the rhythm-control group (absolute difference of 1.3; 90% CI, -1.5 to 4.1). Severe adverse effects of antiarrhythmic drugs occurred in two (0.8%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of -3.7; 90% CI, -6.0 to -1.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks then 200 mg QD vs rate control therapy: digitalis, non-dihydropyridine calcium channel blocker, and β-blocker, alone or in combination				A pacemaker was implanted in three (1.2%) patients in rate-control group and in eight (3.0%) patients in the rhythm-control group (-1.8; 90% CI, -3.9 to 0.2). Secondary: Not reported
Opolski et al.[49] (2004) HOT CAFÉ Rhythm control therapy: propafenone 450 to 600 mg QD, disopyramide 300 to 600 mg QD, or sotalol 160 to 320 mg QD vs rate control therapy: β-blockers, non-dihydropyridine calcium channel blockers, digoxin, or a combination of these drugs.	MC, OL, RCT Patients between 50 to 75 years of age with AF known to be present continuously for between seven days and two years with acceptable etiology of the arrhythmia related to ischemic heart disease, arterial hypertension, hemodynamically insignificant valvular heart disease, or lack of assessable etiology	N=205 1 year	Primary: Composite of death from any cause (thromboembolic complications and intracranial or other major hemorrhage) Secondary: Rate control, sinus rhythm maintenance, discontinuation of therapy (proarrhythmic effects), hemorrhage, hospitalization, new or worsening CHF, or changes in exercise tolerance	Primary: There was not a significant difference in composite of death from any cause between the rate control group and the rhythm control group (OR, 1.98; 95% CI, 0.28 to 22.3; P>0.71). Secondary: The patients in the rhythm control group had a significantly lower mean heart rate (79.1±8.6 beats/min) in 24-hour Holter monitoring compared to the patients in the rate control group (85.8±7.5 beats/min; P<0.003). Four patients in the rhythm control group experienced proarrhythmic effects. Whether this lead to discontinuation of therapy was not mentioned. At the end of the study, 66 patients (63.5%) in the rhythm control arm were in sinus rhythm, with 27 of these patients successfully maintained with the first antiarrhythmic compound administered after the first cardioversion. There was not a statistical difference seen in bleeding complications between the rhythm control group (eight patients) and rate control group (five patients). A significantly lower number of hospitalizations were seen in the rate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients underwent electric cardioversion prior to the initiation of study medication.				control arm compared to the rhythm control arm (12 vs 74%, respectively; P<0.001). Both the rhythm control group and rate control group had significant improvements in CHF class at some point during follow-up compared to baseline (P<0.001 and P<0.05, respectively). No difference in NYHA functional class between patients initially randomized to the two strategies was found at the end of the follow-up period. At the end of the study, both maximal workload and exercise duration were higher in the rhythm control arm compared to the rate control arm (P<0.001 and P<0.001, respectively).
Shelton et al.[50] (2009) CAFE´-II Rhythm control therapy: amiodarone therapy (200 mg TID for 1 month, followed by 200 mg BID for 1 month, followed by 200 mg/day thereafter) vs rate control therapy: digoxin and β-blockers Cardioversion was allowed if patients in the rhythm	MC, RCT Patients >18 years of age with persistent AF and chronic symptomatic heart failure (NYHA >Class II symptoms) with evidence of systolic dysfunction on echocardiography	N=61 1 year	Primary: QOL using the Medical Outcomes Study Short Form-36 version II questionnaire Secondary: Proportion of patients in sinus rhythm, scores on the MLWHF questionnaire, NTproBNP, 6MWT, severity of left ventricular systolic dysfunction	Primary: Patients assigned to rhythm control had a greater improvement in QOL over one year compared to rate control (P=0.020 for Medical Outcomes Study Short Form-36 version II as a whole; P=0.050 for mental functioning and P=0.029 for physical functioning subgroups). Secondary: At one year, target ventricular rate control was achieved in 90% of patients assigned to the rate control group. Digoxin and β-blocker use at one year was 84 and 90%, respectively. All patients in the rate control group were in AF at each and every follow-up visit. Sinus rhythm was restored in 20% of patients using amiodarone alone. Cardioversion restored sinus rhythm in 78% patients in whom it was attempted. Overall, 87% of patients were converted from AF to sinus rhythm at some time during the study. The prevalence of AF in the rhythm control group was 53% at four months, 30% at eight months, and 34% at one year. The difference in QOL using the MLWHF questionnaire was not significant in patients assigned to rhythm control vs rate control (P=0.140). The median NTproBNP concentrations at one year were 1,480 and 685 pg/mL for rate and rhythm groups, respectively. A greater reduction was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
control group remained in AF despite amiodarone therapy.				seen for those in the rhythm control group compared to rate control (P=0.047). The mean change in distance walked at one year was 27 and five meters for rate and rhythm control, respectively (P=0.342). Patients assigned to rhythm control had a greater improvement in left ventricular function over one year compared to patients assigned to rate control (P=0.014).
Lafuente-Lafuente et al.[51] (2009) Antiarrhythmic drugs (amiodarone, aprindine, azimilide, bidisomide, flecainide, disopyramide, dofetilide, dronedarone, quinidine, propafenone, sotalol) vs placebo, drugs for rate control (digoxin, calcium channel blockers, β-blockers) or no treatment	MA (45 trials) Adults >16 years of age who had AF of any type and duration and in whom sinus rhythm had been restored, spontaneously or by any therapeutic intervention	N=12,559 Variable duration	Primary: Mortality, embolic complications, adverse events Secondary: Use of anticoagulation, recurrence of AF	Primary: No deaths were reported with flecainide in the three trials. Quinidine showed a trend to increase mortality compared to controls (OR, 2.26; 95% CI, 0.93 to 5.45; P=0.07). This trend was significant if missing patients were counted as deaths (OR, 2.29; 95% CI, 1.05 to 5.01; P=0.04), and when class IA drugs (quinidine and disopyramide) were combined (OR, 2.39; 95% CI 1.03 to 5.59; P=0.04). The number NNH for class IA drugs was 109 patients treated for one year to have one excess death. Sotalol showed a trend to increased mortality (OR, 2.09; 95% CI, 0.97 to 4.49; P=0.06) compared to controls. This trend was significant if missing patients were counted as deaths (OR, 2.27; 95% CI, 1.36 to 3.77; P=0.002). Amiodarone was associated with a reduction in mortality compared to combined class I drugs (OR, 0.39; 95% CI, 0.19 to 0.79; NNT, 17). When compared to controls, amiodarone showed no significant difference in mortality. No other significant difference in mortality was detected, either vs control or between different antiarrhythmics. The analysis of cardiovascular mortality gave the same results as that of all-cause mortality. Only five of the 30 studies comparing antiarrhythmics with a control reported stroke outcomes. They reported six strokes in 650 patients in the control groups and 20 strokes in 1,755 patients treated with antiarrhythmics.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Withdrawals due to adverse effects were more frequent with all drugs, except aprindine and dofetilide, compared to controls. Pooled events rates varied from 9 to 23% for withdrawals due to adverse effects. The mean number of patients needed to treat for one year to have one excess withdrawal from treatment ranged from nine (quinidine) to 27 (amiodarone, propafenone, or sotalol). Quinidine caused more withdrawals than the other class I drugs (OR, 2.25; 95% CI 1.45 to 3.51; P=0.0003). Amiodarone produced significantly fewer withdrawals than other class I drugs combined (OR, 0.52; 95% CI, 0.34 to 0.81; P=0.004). All antiarrhythmics increased proarrhythmic effects, with the exception of amiodarone and propafenone. Pooled events rates varied from 1 to 7% for proarrhythmia. The NNH for proarrhythmia ranged between 17 (flecainide) and 119 (dofetilide). Amiodarone produced significantly less proarrhythmic events than other class I drugs combined (OR, 0.28; 95% CI, 0.13 to 0.59; P=0.0007). Secondary: All class IA, class IC and class III drugs significantly reduced the recurrence of AF. Pooled recurrence rates of AF at one year were 71 to 84% in controls and were reduced to 42% to 67% in patients treated with antiarrhythmics. The NNT for one year to avoid one recurrence of AF were three with amiodarone, four with flecainide, five with dofetilide and propafenone, eight with quinidine and sotalol and 10 with dronedarone. Amiodarone reduced recurrences of AF significantly more than combined class I drugs (OR, 0.31; 95% CI, 0.21 to 0.45; P<0.0001) and more than sotalol (OR, 0.43; 95% CI 0.29 to 0.64; P<0.0001). No other differences between antiarrhythmics were detected. Chronic anticoagulation with warfarin was mandatory in only three studies. The decision on anticoagulation was left to the judgment of the attending physician in the remaining studies.

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, SB=single-blinded

Miscellaneous abbreviations: 6MWT=6-minute corridor walk test, AD=arrhythmic death, AF=atrial fibrillation, AT=atrial tachyarrhythmias, CABG=coronary artery bypass graft, CHF=congestive heart failure, CI=confidence interval, ECG=electrocardiographic, HR=hazard ratio, LVEF=left ventricular ejection fraction, MI=myocardial infarction, MLWHF=Minnesota Living with Heart Failure, MUGA=multiple-gated nuclear angiography, NNH=number needed to harm, NNT=number needed to treat, NTproBNP=N-terminal prohormone of brain natriuretic peptide, NYHA=New York Heart Association, OR=odd ratio, QOL=quality of life, RR=relative risk, RVF=resuscitated ventricular fibrillation, SF-12=12-Item Short Form Health Survey, SND=sinus node disease, TIA=transient ischemic attack, VDPs=ventricular premature depolarizations, VT=ventricular tachycardia

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 15. Relative Cost of the Antiarrhythmic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amiodarone	injection, tablet	Cordarone®*, Nexterone®, Pacerone®*	$	$
Disopyramide	capsule, extended-release capsule	Norpace®*, Norpace CR®	$$$-$$$$$	$-$$$
Dofetilide	capsule	Tikosyn®	$$$$$	N/A
Dronedarone	tablet	Multaq®	$$$$$	N/A
Flecainide	tablet	Tambocor®*	$$$$-$$$$$	$
Mexiletine	capsule	N/A	N/A	$
Propafenone	extended-release capsule, tablet	Rythmol®*, Rythmol SR®*	$$$$$	$$
Quinidine	extended-release tablet, injection, tablet	N/A	N/A	$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The antiarrhythmic agents are effective for the treatment of atrial fibrillation/flutter and ventricular arrhythmias. These agents differ with regards to their Food and Drug Administration (FDA)-approved indications, mechanism of action, pharmacokinetic properties, drug interactions and adverse events. All of the antiarrhythmic agents are available in a generic formulation, with the exception of dofetilide and dronedarone.

There are several guidelines that provide recommendations on the use of antiarrhythmic agents for the treatment of both atrial and ventricular arrhythmias. The antiarrhythmics are generally not recommended as first-line agents for the treatment of ventricular arrhythmias. Amiodarone and sotalol may be used to treat ventricular tachycardias in patients with left ventricular dysfunction due to a prior myocardial infarction (MI) and who are not responding to β-blockade from other agents. In those patients with atrial fibrillation (AF), rate control is the recommended treatment strategy but rhythm control may be appropriate in certain circumstances, particularly in patients whose quality of life is affected by AF. Some antiarrhythmic agents may be appropriate to use for rhythm control in patients with particular disease states, for instance sotalol and Class IA antiarrhythmics may be used for postoperative AF or atrial flutter in patients with coronary artery disease without congestive heart failure.[3-8] Overall, the AFFIRM, RACE, and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control strategies.[5, 47-49] There are many factors that should be addressed prior to the selection of an antiarrhythmic agent for a patient, including the type of arrhythmia, concurrent disease states, and potential risk to benefit ratio of therapy. These agents have not been shown to improve mortality in patients with atrial or ventricular arrhythmias.[3-8]

Amiodarone is an effective treatment option for AF; however, its use is limited by toxicity (pulmonary, thyroid and gastrointestinal), photosensitivity reactions, and bluish discoloration of the skin. Amiodarone is associated with a low risk of proarrhythmia in patients with left ventricular hypertrophy, heart failure, coronary artery disease, and previous MI.[11,17,19] Trials also support the efficacy of dofetilide for the prevention of atrial fibrillation/flutter. To reduce the risk of early proarrhythmia, dofetilide must be initiated in the hospital. Dofetilide is available only to hospitals and prescribers who have received appropriate dofetilide dosing and treatment initiation education.[18,19]

Dronedarone is a new antiarrhythmic agent, which was approved by the FDA in July 2009. It is a non-iodinated analog of amiodarone, and as a result, it is less lipophilic and has a shorter half-life than amiodarone. These structural changes were made to reduce the risk of thyroid and pulmonary toxicity. Clinical trials have shown that dronedarone reduces the risk of recurrent atrial fibrillation/flutter and is effective for the long-term maintenance of sinus rhythm.[30,31,37] However, the ANDROMEDA trial was terminated early due to an excess number of deaths in patients with heart failure who received dronedarone. Death from any cause occurred in 8.1% of patients receiving dronedarone and 3.8% of patients receiving placebo (hazard ratio, 2.13; 95% confidence interval, 1.07 to 4.25; P=0.03).[35] As a result, dronedarone is contraindicated in patients with New York Heart Association (NYHA) class IV heart failure or NYHA class II to III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.[12] In a comparative study, dronedarone was found to be less effective than amiodarone for the composite end point of AF recurrence or premature drug discontinuation for intolerance or lack of efficacy. There were fewer thyroid and neurological adverse events with dronedarone, as well as fewer patients discontinuing therapy due to adverse events compared to amiodarone.[41,52] There were no studies found in the medical literature which evaluated the use of dronedarone for the prevention or treatment of ventricular arrhythmias. In December 2011, the FDA released a safety warning regarding an increased risk of death or serious cardiovascular events with dronedarone. A completed safety review, which included data from the PALLAS and ATHENA trials, demonstrated that dronedarone increased the risk of serious cardiovascular events, including death, when used by patients in permanent AF. Based on the findings of the FDA safety review, the approved package labeling changed to include additional recommendations for the use of dronedarone in patients with non-permanent.

There is insufficient evidence to support that one brand antiarrhythmic agent is more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antiarrhythmic agents within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand antiarrhythmic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cardiotonic Agents
AHFS Class 240408
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I. Overview

Digoxin is the only cardiotonic agent that is currently available. It inhibits sodium-potassium ATPase, which increases the intracellular concentration of sodium and calcium. This leads to an increase in the force/velocity of myocardial contractions, decreased activation of the sympathetic nervous system and renin-angiotensin system, as well as a decrease in heart rate and conduction velocity through the atrioventricular node. Digoxin is an effective treatment for heart failure due to its positive inotropic and neurohormonal deactivating effects. It is also beneficial for atrial arrhythmias due to its vagomimetic actions. In high doses, digoxin increases sympathetic outflow from the central nervous system, which may lead to toxicity.[1-3]

The cardiotonic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Digoxin injection, solution and tablets are all available in a generic formulation. This class was last reviewed in August 2010.

Table 1. Cardiotonic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Digoxin	injection, solution, tablet	Lanoxin®*, Lanoxin Pediatric®	digoxin

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cardiotonic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cardiotonic Agents

Clinical Guideline	Recommendation(s)
American College of Cardiology/American Heart Association/ European Society of Cardiology Committee for Practice Guidelines: **Focused Updated on the Management of Patients with Atrial Fibrillation (Updating 2006 Guideline)[4] (2011)**	• Oral digoxin may effectively control the heart rate at rest in patients with atrial fibrillation (AF) and is indicated for patients with heart failure, left ventricular dysfunction, or for sedentary individuals. • Digoxin is no longer considered first-line therapy for rapid management of AF, except in patients with heart failure or left ventricular dysfunction, or perhaps in patients who are so sedentary as to obviate the need for rate control during activity because there are more effective agents that are now available. • To control heart rate, digoxin use concurrently with either a β-blocker or nondihydropyridine calcium channel blocker is reasonable in patients with AF, both at rest and during exercise. The medication chosen should be individualized and bradycardia should be avoided by closely monitoring and changing digoxin therapy. • Concurrent use of digoxin and β-blockers appears to be more effective than the concurrent use of digoxin and a calcium channel blocker. • It is not recommended to use digoxin for pharmacological cardioversion of AF as harm may be caused. • Digitalis glycosides have not been proven to be more efficacious than placebo for the conversion of recent-onset AF to sinus rhythm. Digoxin may actually prolong the duration of paroxysmal AF episodes in some patients. • Evidence does not support the use of digitalis to suppress recurrent AF

Clinical Guideline	Recommendation(s)
	in most patients. • Digoxin, a β-blocker, or a nondihydropyridine calcium channel blocker are all options and are recommended in pregnancy to control ventricular response rate.
National Institute for Health and Clinical Excellence: **Atrial Fibrillation[5] (2006)**	• For patients who need rate control for chronic AF, β-blockers and calcium channel blockers are first line agents. Digoxin should only be used as first line in sedentary patients or in those who cannot tolerate β-blockers or calcium channel blockers. • For patients who are prescribed digoxin alone for rate control, a diagnosis should be written on the prescription. • Combination therapies such as digoxin and β-blocker or digoxin and calcium channel blocker may be considered once a patient has failed monotherapy. • Digoxin has been proven to be ineffective in pharmacological cardioversion and therefore is determined to be an inappropriate therapy for this indication. • Digoxin should not be used in AF patients who are hemodynamically unstable due to its slow onset of action. • The use of digoxin in patients with Wolff-Parkinson-White syndrome is contraindicated due to the potential of exacerbating a rapid AF. • Digoxin has not been clinically proven to be effective in preventing postoperative AF therefore should not be used in this indication.
American College of Chest Physicians: **Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery[6] (2005)**	• β-blockers and nondihydropyridine calcium channel blockers are recommended as first- and second-line agents to control ventricular response rate in AF after cardiac surgery. Digoxin has shown little efficacy in this patient population. • Current medical evidence does not support the use of digitalis for the prevention of postoperative AF. • No recommendation can be made regarding the use of digoxin for rhythm control of postoperative AF or atrial flutter.
American Academy of Family Physicians/American College of Physicians: **Management of Newly Detected Atrial Fibrillation[7] (2003)**	• For patients AF, the following drugs are recommended for their demonstrated efficacy in rate control during exercise and while at rest: atenolol, metoprolol, diltiazem, and verapamil. Digoxin is only effective for rate control at rest and therefore should only be used as a second-line agent for rate control in atrial fibrillation. • Combinations of digoxin plus diltiazem, atenolol, or betaxolol have also been shown to be effective at rest and with exercise, but these may be better reserved for occasions when single agent therapy has failed.
American College of Cardiology/American Heart Association: **Guideline Update for the Diagnosis and Management of Chronic Heart Failure in Adults[8] (2009; Focused Update)**	• The safety and efficacy of digoxin does not compare favorably with that of other agents such as aldosterone blockers. • Digoxin may be added to concurrent therapy with diuretics, an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and a β-blocker in those patients with persistent heart failure symptoms or in those patients who have not yet responded to this initial therapy. • Digoxin therapy may be delayed until the patient remains symptomatic despite therapy with the neurohormonal antagonists or delay digoxin therapy until the symptomatic patient has tried and did not respond or could not tolerate aldosterone antagonist as well. • Digoxin should be considered an adjunct therapy to β-blockers for rate control because β-blockers improve survival and may be effective at controlling rate alone. • In patients with an acute exacerbation of heart failure symptoms, the patient should be initially treated with appropriate heart failure therapy, and once stable, digoxin may be initiated as part of a long-

Clinical Guideline	Recommendation(s)
	term treatment plan. • Digoxin should be avoided in patients with significant sinus or atrioventricular block (unless patient has pacemaker) and it should be used cautiously in patients who are on other agents that may suppress sinus or atrioventricular nodal function or affect digoxin levels.

Institute for Clinical Systems Improvement:
Heart Failure in Adults[9] (2011)
	Pharmacologic management:
	• Carvedilol, metoprolol succinate (extended-release) and bisoprolol have demonstrated reductions in mortality for patients with all classes of heart failure. These agents should be used before using other generic β-blockers.
	• ACE inhibitors should be prescribed for all patients with left ventricular systolic dysfunction unless contraindications are present.
	• If non-African American, ACE inhibitors are recommended for decreasing heart failure mortality than isosorbide dinitrate/hydralazine. In contrast, combination hydralazine and nitrates is recommended for patients self-described as African Americans, with moderate to severe symptoms on optimal therapy with ACE inhibitors, β-blockers, and diuretics.
	• ARBs should be considered primarily for patients who are intolerant to ACE inhibitors or in patients receiving standard drug therapy (including ACE inhibitors) who continue to show clinical deterioration.
	• Routine use of ARBs and ACE inhibitors and aldosterone antagonists cannot be recommended.
	• Diuretics should not be the sole therapy for patients with signs of volume overload; vasoactive drugs should be considered.
	• In severe heart failure, loop diuretics should be used over thiazide diuretics and combination therapy with thiazide. Loop diuretics are also effective in refractory cases of volume overload.
	• Patients with New York Heart Association (NYHA) class III-IV heart failure on stable doses of digoxin and ACE inhibitors can reduce mortality by administering aldosterone-blocking agents.
	• Nesiritide is recommended to be reserved for patients with decompensated heart failure who remain volume overloaded despite aggressive treatment with diuretics/vasodilators display tolerance and/or resistance to vasodilators or diuretics, or demonstrate significant side effects to other vasodilators.
	• When considering the use of calcium channel blockers, only dihydropyridine calcium channel blockers have been shown safe. Non-dihydropyridine calcium channel blockers can be used in patients with preserved systolic heart failure.
	
	Pharmacologic management-digoxin
	• In patients in normal sinus rhythm with preserved systolic function and mild to moderate heart failure symptoms on optimal therapy, digoxin had no effect on the endpoints of all-cause or cardiovascular mortality or hospitalization.
	• Serum levels less than 1.0 ng/mL are considered therapeutic. Levels greater than 1.2 have been associated with greater side effects. Serum levels do not always correlate to symptoms of digoxin toxicity.
	• Digoxin has been found useful:
	    ○ In heart failure patients with atrial fibrillation with a rapid ventricular response.
	    ○ In combination with ACE inhibitors in reducing hospitalizations in heart failure patients.

Clinical Guideline	Recommendation(s)

	• Digoxin should not:
	  ○ Be initiated in asymptomatic heart failure patients as it remains unsupported by clinical trials.
	  ○ Be "loaded" either orally or intravenously. Loading doses are generally not needed and steady state generally takes one week to reach.
	• Monitor for symptoms of toxicity, reduction of renal function or conduction abnormality.
	• To avoid digitalis toxicity, use lower doses in the elderly and those with renal impairment, check level in one to two weeks after start of therapy in elderly or renal-impaired patients, and be aware of drug interactions with new medications.
	• If continuing digoxin therapy in women, it may be reasonable to recommend that lower dosing (0.125 mg/day) should be used and lower serum levels (1.0 or less) should be maintained.

Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines[10] (2010)**	• Digoxin should be considered for patients with left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%) who have signs or symptoms of heart failure while receiving standard therapy, including ACE inhibitors and β-blockers. • It is recommended that the dose of digoxin, which should be based on lean body mass, renal function and concomitant medications, should be 0.125 mg daily in the majority of patients and the serum digoxin level should be <1.0 ng/mL, generally 0.7 to 0.9 ng/mL. • Doses >0.25 mg daily, for the purpose of rate control, are not recommended. • Digoxin should be considered for adequate control of the ventricular response to AF in patients with heart failure. • For patients taking amiodarone and digoxin concurrently, it is recommended that the maintenance dose of digoxin be reduced when amiodarone is initiated and then carefully monitored for the possibility of adverse drug interactions. Adjustment in doses of these drugs and laboratory assessment of drug activity or serum concentration after initiation of amiodarone is recommended.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[11] (2012)**	Treatment of acute heart failure • In patients with reduced ejection fraction, digoxin may be used to control (slow) the ventricular rate in AF, especially if it has not been possible to up-titrate the dose of β-blocker. • Digoxin may provide symptom benefit and reduce the risk of heart failure hospitalizations in patients with severe systolic heart failure. Arrhythmias, bradycardia, and atrioventricular block in patients with heart failure with reduced ejection fracture and heart failure with preserved ejection fracture-rate control • For rate control in patients with heart failure-reduced ejection fraction, a β-blocker is preferred over digoxin as the latter does not provide rate control during exercise. β-blockers also have a favorable effect on mortality and morbidity in systolic heart failure per se. The combination of digoxin and a β-blocker is more effective than a β-blocker alone in controlling the ventricular rate at rest. • In patients with heart failure-preserved heart failure, rate-limiting calcium channel blockers are an effective alternative to a β-blocker. The combination of digoxin and a rate-limiting calcium channel blocker is more effective than a calcium channel blocker alone in controlling the ventricular rate at rest.

Clinical Guideline	Recommendation(s)
	Treatments with less certain benefits in patients with symptomatic (NYHA class II-IV) systolic heart failure • Digoxin may be considered to reduce the risk of heart failure hospitalization in patients in sinus rhythm with an ejection fraction ≤45% who are unable to tolerate a β-blocker. Patients should also receive an ACE inhibitor (or ARB) and a mineralocorticoid receptor antagonist (or ARB). • Digoxin may be considered to reduce the risk of heart failure hospitalization in patients with an ejection fraction ≤45% and persisting symptoms (NYHA Class II-IV) despite treatment with a β-blocker, ACE inhibitor (or ARB), and an mineralocorticoid receptor antagonist (or ARB).

National Institute for Health and Clinical Excellence: **Chronic Heart Failure: National Clinical Guidelines for Diagnosis and Management in Primary and Secondary[12] Care (2010; Partial Update)**	Heart failure due to left ventricular systolic dysfunction
	• As first-line treatment, offer both ACE inhibitors and β-blockers licensed for heart failure to all patients.
	• As second-line treatment, seek advice from a specialist and consider adding one of the following remains symptomatic despite optimal therapy with ACE inhibitor or a β-blocker:
	  ○ An aldosterone antagonist licensed for heart failure (especially moderate or severe heart failure or previous MI within the past month).
	  ○ An ARB licensed for heart failure (especially mild to moderate heart failure).
	  ○ Hydralazine in combination with nitrate (especially if patient is African American or Caribbean origin and moderate to severe heart failure).
	• Hydralazine in combination with nitrate may be used first-line in patients intolerant to ACE inhibitors and ARBs.
	• ARBs may be used first-line in patients intolerant to ACE inhibitors.
	• Digoxin is recommended for worsening or severe heart failure due to left ventricular systolic dysfunction despite first- and second-line treatment for heart failure.
	
	Monitoring
	• Routine monitoring of serum digoxin concentrations is not recommended. A digoxin concentration measured within eight to 12 hours of the last dose may be useful to confirm a clinical impression of toxicity or non-adherence.
	• The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic' range.

National Institute for Health and Clinical Excellence: **Management of Chronic Heart Failure in Adults in Primary and Secondary Care[13] (2003)**	• First line therapy for patients with heart failure is an ACE inhibitor or ARB (if ACE inhibitor is not tolerated). • Digoxin may be added to concurrent therapy with a diuretic, ACE inhibitor, ARB, or β-blocker if the patient remains symptomatic and is in sinus rhythm. • If a patient has symptomatic heart failure and atrial fibrillation, digoxin should be used as the first line agent. • Digoxin is recommended for patients with worsening or severe heart failure due to left ventricular systolic dysfunction despite therapy with ACE inhibitor, β-blocker and diuretic therapy. • Digoxin is recommended in patients with atrial fibrillation and any degree of heart failure. • Serum potassium should be monitored when patients are on digoxin therapy.

Clinical Guideline	Recommendation(s)
	• It is not recommended to obtain serum digoxin levels on a routine basis. A digoxin level drawn between 8 to12 hours after the last dose may supply useful information to determine toxicity or non-compliance. • Reminder that patient's may experience signs of toxicity even if there digoxin level is in the recommended therapeutic range.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cardiotonic agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Cardiotonic Agents[1-3]

Indication	Digoxin
Control of ventricular response rate in patients with chronic atrial fibrillation	✔ *
Increase myocardial contractility in pediatric patients with heart failure	✔ †
Treatment of mild to moderate heart failure in adults	✔

*Tablet is approved for adult patients.
†Tablet only.

IV. Pharmacokinetics

The pharmacokinetic parameters of the cardiotonic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cardiotonic Agents[14]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (days)
Digoxin	60 to 80 (oral)	20 to 25	Liver (16)	Renal (57 to 80) Bile (6 to 8) Feces (3 to 5)	1.3 to 2.2

V. Drug Interactions

Significant drug interactions with the cardiotonic agents are listed in Table 5.

Table 5. Significant Drug Interactions with the Cardiotonic Agents[3]

Generic Name(s)	Significance Level	Interaction	Mechanism
Digoxin	1	Aminoglycosides	The mechanism of this interaction is unknown. The rate and extent of digoxin absorption may be reduced, which could reduce the pharmacologic effect of the drug.
Digoxin	1	Amiodarone	Serum digoxin levels may be increased, resulting in an increase in the pharmacologic and toxic effects of digoxin. Mechanism of interaction is unknown.
Digoxin	1	Cyclosporine	Mechanism of interaction unknown. The

Generic Name(s)	Significance Level	Interaction	Mechanism
			pharmacologic effects of digoxin may be increased, possibly leading to toxicity.
Digoxin	1	Loop diuretics	Increased urinary excretion of potassium and magnesium affecting cardiac muscle action, and other factors may also be involved. Diuretic-induced electrolyte disturbances may predispose patients to digoxin-induced arrhythmias.
Digoxin	1	Macrolides and ketolides	Macrolides and ketolides may increase serum concentrations and toxic effects of digoxin. Inhibition of the P-glycoprotein transport system by macrolides and ketolides may increase the oral absorption and reduce the renal secretion of digoxin. Macrolides and ketolides-related alterations in gut flora may also play a role.
Digoxin	1	Paroxetine	Inhibition of renal tubular P-glycoprotein excretion of digoxin by paroxetine is suspected, increasing digoxin serum concentrations, increasing the pharmacologic and toxic effects.
Digoxin	1	Protease inhibitors	Protease inhibitors may increase plasma concentrations and pharmacologic effects of digoxin. Although the exact mechanism is unknown, P-glycoprotein inhibition by protease inhibitors may enhance the absorption and decrease the renal excretion of digoxin.
Digoxin	1	Propafenone	Actual mechanism of the interaction is unknown. The volume of distribution of digoxin may be decreased along with a decrease in the renal and non-renal clearance which may increase serum digoxin levels, resulting in toxicity.
Digoxin	1	Quinidine	Quinidine may reduce the renal clearance, biliary clearance and volume of distribution of digoxin thereby increasing serum digoxin levels and increasing the risk of toxicity.
Digoxin	1	Tetracyclines	Tetracycline may reverse the process by which digoxin is metabolized by gastrointestinal flora by altering gastrointestinal flora, allowing for more digoxin to be absorbed and increasing digoxin serum levels.
Digoxin	1	Thiazide diuretics	Increased urinary excretion of potassium and magnesium affecting cardiac muscle, and other factors may be involved. Thiazide-induced electrolyte disturbances may predispose to digoxin-induced arrhythmias.
Digoxin	1	Verapamil	Verapamil may alter the pharmacokinetics and increase serum

Generic Name(s)	Significance Level	Interaction	Mechanism
			concentrations of digoxin. Toxicity characterized by gastrointestinal symptoms, neuropsychiatric symptoms, and cardiac arrhythmias may result.
Digoxin	2	Acarbose	Pharmacologic effects and plasma concentrations of digoxin may be decreased by acarbose. The mechanism of this interaction is unknown.
Digoxin	2	Activated charcoal	Charcoal can reduce gastrointestinal absorption of many drugs and actually remove drugs from the systemic circulation which will reduce the effectiveness or toxicity of a given agent.
Digoxin	2	Aminoglycosides	Pharmacologic effects of digoxin may be increased or decreased due to altered bioavailability.
Digoxin	2	Antineoplastic agents	Drug-induced alterations of the intestinal mucosa may be involved in reduced gastrointestinal absorption of digoxin; therefore, serum levels of digoxin may be reduced and actions may be decreased.
Digoxin	2	β-blockers	Carvedilol may increase digoxin bioavailability. Possible additive depression of myocardial conduction and decreased renal tubular digoxin secretion may occur. Serum digoxin concentrations may be increased by coadministration of carvedilol. Synergistic bradycardia may occur in some patients.
Digoxin	2	Cholestyramine	Bioavailability and pharmacologic effects of digoxin may be decreased by bile acid sequestrants. The gastrointestinal absorption of digoxin may be decreased due to formation of a physical or chemical complex with bile acid sequestrants.
Digoxin	2	Colestipol	Colestipol may physically bind with digoxin and cause a decrease in its gastrointestinal absorption and normal enterohepatic recycling. Colestipol may decrease the half-life of digoxin, possibly reducing its therapeutic effect.
Digoxin	2	Diltiazem	Pharmacologic effects of digoxin may be increased by diltiazem. Elevated digoxin serum concentrations and toxicity, characterized by gastrointestinal and neuropsychiatric symptoms and cardiac arrhythmias, may occur. Pharmacodynamic effects of diltiazem and digoxin may be additive. The clearance of digoxin may be decreased by diltiazem.
Digoxin	2	Dronedarone	Plasma concentrations and

Generic Name(s)	Significance Level	Interaction	Mechanism
			pharmacologic effects of digoxin may be increased due to inhibition of P-glycoprotein (P-gP) efflux transport by dronedarone. Digoxin may also enhance the electrophysiologic effects of dronedarone.
Digoxin	2	Indomethacin	Serum concentrations and pharmacologic effects of digoxin may be increased by indomethacin. By decreasing renal blood flow, indomethacin may decrease renal elimination of digoxin.
Digoxin	2	Itraconazole	Itraconazole may increase pharmacologic effects and plasma concentrations of digoxin by decreasing renal the renal excretion of digoxin; toxicity may occur.
Digoxin	2	Metoclopramide	By increasing gastrointestinal motility, metoclopramide may decrease the plasma levels of digoxin, decreasing therapeutic effects. This interaction may not occur with high-bioavailability digoxin formulations.
Digoxin	2	Penicillamine	Pharmacologic effects of digoxin may be decreased. Reduced digoxin serum levels, possibly with a suboptimal therapeutic response may result. The mechanism of this interaction is unknown.
Digoxin	2	Quinine	Quinine may increase digoxin serum concentrations. Toxicity characterized by gastrointestinal and neuromuscular symptoms, and cardiac arrhythmias may occur.
Digoxin	2	Spironolactone	Spironolactone may attenuate the positive inotropic effect of digoxin. Serum levels of digoxin also may be increased. Additionally, spironolactone may interfere with the digoxin radioimmunoassay, resulting in falsely elevated digoxin levels.
Digoxin	2	Thioamines	Thioamines may alter pharmacologic effects and plasma concentrations of digoxin. The mechanism of this interaction is unknown.
Digoxin	2	Thyroid hormones	The therapeutic effectiveness of digoxin may be decreased, with possible exacerbation of cardiac arrhythmias or congestive heart failure. The mechanism of this interaction is unknown.

Significance Level 1 = major severity.
Significance Level 2 = moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the cardiotonic agents are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Cardiotonic Agents[3,14]

Adverse Events	Digoxin
Cardiovascular	
Cardiac dysrhythmia	✔
Heart arrest	1
Palpitation	1
Tachycardia	2
Ventricular extrasystole	1
Central Nervous System	
Apathy	✔
Confusion	✔
Dizziness	6
Headache	4
Mental disturbances	5
Weakness	✔
Gastrointestinal	
Abdominal pain	✔
Anorexia	1
Diarrhea	4
Hemorrhagic necrosis of the intestines	✔
Intestinal ischemia	✔
Nausea	4
Vomiting	2
Other	
Death	4
Gynecomastia	✔
Macropapular rash	✔
Other skin reactions	2
Thrombocytopenia	✔

✔ Percent not specified.

VII. Dosing and Administration

The usual dosing regimens for the cardiotonic agents are listed in Table 7. Several factors must be taken into account when dosing digoxin, including the patient's lean body weight, renal function, age, concomitant disease states, concurrent medications, and other factors that may alter the pharmacokinetic properties of digoxin.[4-5]

Table 7. Usual Dosing Regimens for the Cardiotonic Agents[1-3,14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Digoxin	<u>Control of ventricular response rate in patients with chronic atrial fibrillation:</u> Injection, solution: doses should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects Tablet: dose is based on	<u>Control of ventricular response rate in patients with chronic atrial fibrillation:</u> Injection, solution doses should be titrated to the minimum dose that achieves the desired ventricular rate control without causing undesirable side effects	Injection*: 100 µg/mL 250 µg/mL Solution: 50 µg/mL Tablet: 125 µg 250 µg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose (10 to 15 µg/kg) followed by maintenance dosing (3.4 to 5.1 µg/kg/day) if rapid titration is desired OR initiated with maintenance dosing (3.4 to 5.1 µg/kg/day) without a loading dose <u>Treatment of mild to moderate heart failure:</u> Injection, solution: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose followed by maintenance dosing if rapid titration is desired OR initiated with maintenance dosing without a loading dose Tablet: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose (10 to 15 µg/kg) followed by maintenance dosing (3.4 to 5.1 µg/kg/day) if rapid titration is desired OR initiated with maintenance dosing (3.4 to 5.1 µg/kg/day) without a loading dose	<u>Increase myocardial contractility in pediatric patients with heart failure in children >10 years of age:</u> Tablet: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose (10 to 15 µg/kg) followed by maintenance dosing (3.4 to 5.1 µg/kg/day) if rapid titration is desired OR initiated with maintenance dosing (3.4 to 5.1 µg/kg/day) without a loading dose <u>Increase myocardial contractility in pediatric patients with heart failure in children 5 to 10 years of age:</u> Tablet: dose is based on patient-specific factors (e.g., age, lean body weight, renal function, etc); dosing can be either initiated with a loading dose (20 to 45 µg/kg) followed by maintenance dosing (6.4 to 12.9 µg/kg/day OR 3.2 to 6.4 µg/kg/day twice daily) if rapid titration is desired OR initiated with maintenance dosing (3.4 to 5.1 µg/kg/day) without a loading dose <u>Treatment of mild to moderate heart failure:</u> Injection, solution: dosage guidelines provided in prescribing information are based upon average patient response and substantial individual variation can be expected; ultimate dosage selection must be based upon clinical assessment of the patient	

*Parenteral administration of digoxin should be used only when the need for rapid digitalization is urgent or when the drug cannot be taken orally. Intramuscular injection can lead to severe pain at the injection site; therefore, intravenous administration is preferred. If the drug must be administered by the intramuscular route, it should be injected deep into the muscle followed by massage.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cardiotonic agents are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Cardiotonic Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atrial Fibrillation				
Hallberg et al.[15] (2007) AF group: Patients with atrial fibrillation on digoxin vs patients with atrial fibrillation not on digoxin CHF group: patients with CHF on digoxin vs patients with CHF not on digoxin AF and CHF group: Patients with atrial fibrillation and CHF on digoxin vs patients with AF and CHF not on	Cohort AF group: ECG finding of atrial fibrillation at admission, at discharge or had a discharge diagnosis of atrial fibrillation CHF group: History of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission AF and CHF group: ECG finding of atrial fibrillation on admission, ECG finding of atrial fibrillation at discharge or a discharge diagnosis of atrial fibrillation, and a medical history of CHF, a diagnosis of CHF at discharge or pulmonary edema on admission	N=60,764 1 year	Primary: One year mortality Secondary: Effects on LVEF, s-creatinine and AMI	Primary: Patients with AF who received digoxin did significantly worse than those AF patients who did not receive digoxin therapy (RR of death was 1.42; 95% CI, 1.29 to 1.56). Patients with CHF who received digoxin therapy did significantly worse than those CHF patients who did not receive digoxin therapy (RR of death was 1.11; 95% CI, 1.04 to 1.19). In the group of patients with AF and CHF, there was no mortality difference between those that received digoxin therapy and those that did not receive digoxin therapy (RR of death was 1.00; 95% CI, 0.94 to 1.06). Secondary: In patients with an LVEF of ≤30%, there was not a significant difference in rate of death between patients who received digoxin therapy and those that did not (RR of death was 1.06; 95% CI, 0.86 to 1.31). In patients with an LVEF of >30%, there was not a significant difference in rate of death between patients who received digoxin therapy and those that did not (RR of death was 1.14; 95% CI, 0.98 to 1.32). Regardless of level of s-creatinine (low, normal, high), there was not a significant difference in mortality between those who received digoxin therapy and those who did not: low s-creatinine (RR of death was 1.23; 95% CI, 0.91 to 1.66), normal s-creatinine (RR of death was 1.22; 95% CI, 0.94 to 1.58), high s-creatinine (RR of death was 0.98; 95% CI, 0.83 to 1.16) respectively. In patients with an AMI, the RR for death was 1.17; 95% CI, 1.10 to 1.24 between those that received digoxin therapy and those that did not receive digoxin therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
digoxin				In patients without an AMI, the RR for death was 1.10; 95% CI, 1.04 to 1.16 between those that received digoxin therapy and those that did not receive digoxin therapy.
Khand et al.[16] (2003) Phase 1: Digoxin with placebo vs digoxin with carvedilol Phase 2: digoxin vs carvedilol	DB, PC, PG, RCT Patients with persistent AF for >1 month and heart failure who were receiving digoxin and diuretics	N=47 Phase 1: 4 months Phase 2: 6 months	Primary: Assessment of LVEF, ventricular rate control, symptom improvement, exercise test Secondary: Not reported	Primary: *Phase 1:* The patients in the digoxin with carvedilol group experienced a reduction in mean ventricular rate compared to the patients in the digoxin with placebo group (65.2±15 vs 74.9±11.2, respectively; P<0.0001). The patients in the digoxin with carvedilol group experienced improved LVEF compared to the patients in the digoxin with placebo group (30±9.6 vs 26±12.4, respectively; P=0.048). The patients in the digoxin with carvedilol group experienced an improvement in symptom scores compared to the patients in the digoxin with placebo group (7 [3 to 12.5] vs 8 [3 to 15], respectively; P=0.039). The patients in the digoxin with carvedilol group experienced a reduced ventricular rate at rest and throughout steady-state exercise (peak ventricular rate 106 beats/min) compared to those patients in the digoxin with placebo group (peak ventricular rate 123 beats/min; P<0.05). *Phase 2:* There was no significant difference in ventricular rate control between the digoxin and the carvedilol treatment groups (88.8±18.7 vs 75.7±10.6, respectively; P=0.13). There was no significant difference in LVEF between the digoxin and the carvedilol treatment groups (21.6±11 vs 27.2±11.7, respectively; P=0.15). There was no significant difference in symptom scores between the digoxin and the carvedilol treatment groups (6 [2 to 17] vs 8 [5 to 15.5], respectively; P=0.08). There was no significant difference in ventricular rate at steady-state exercise between the digoxin and the carvedilol treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Koh et al.[17] (1995) Digoxin 0.125 to 0.5 mg QD plus diltiazem 90 mg BID vs digoxin 0.125 to 0.5 mg QD plus betaxolol QD	PRO, RCT, XO Patients with persistent AF for >1 month	N=37 7 months	Primary: Effects on ventricular rate, BP, rate-pressure, maximal exercise tolerance Secondary: Safety	Primary: Patients in the digoxin plus betaxolol group experienced a significant reduction in ventricular rates both at rest and during exercise (67±3 and 135±5 beats/min, respectively) compared to the patients in the digoxin plus diltiazem group (80±7 and 154±5 beats/min, respectively; P<0.05). Patients in the digoxin plus betaxolol group experienced a significant reduction in SBP during maximal exercise (164±4 mm Hg) but not at rest (127±3 mm Hg) compared to the patients in the digoxin plus diltiazem group (173±4 and 130±4 mm Hg, respectively; P<0.05, P>0.05, respectively). Patients in the digoxin plus betaxolol group experienced significantly less rate-pressure products at rest (85±4 x 10^2 mm Hg/min) and during exercise (213±12 x 10^2 mm Hg/min) compared to the patients in the in digoxin plus diltiazem group (105±6 and 269±12, respectively; P<0.05 for both). Both the digoxin plus betaxolol group and the digoxin plus diltiazem group experienced a significant improvement in exercise capacity compared to baseline (P<0.05), but the groups were not statistically significant from one another (9.3±0.5 vs 9.7±0.5 MET; P>0.05). There were no statistical differences between the treatment groups in any of the efficacy points measured between time points at weeks four and seven months. Secondary: No patients withdrew from the study in either treatment groups due to side effects. The digoxin plus betaxolol group experienced more side effects, which were considered minimal, compared to the digoxin plus diltiazem group. The minimal side effects observed in the digoxin plus betaxolol group included dyspnea, gastric pain, fatigue and constipation.
Hemels et al.[18] (2006) Group 1: Digoxin 0.125 to 0.25 mg QD plus acute (within 24 hours) ECV	MC, PRO, RCT Patients with persistent AF, defined as non–self-terminating arrhythmia and requiring ECV to	N=144 18 months	Primary: Freedom from permanent AF Secondary: QOL	Primary: At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent AF between the acute and routine ECV groups (32%; 95% CI, 22 to 44 vs 31%; 95% CI, 21 to 44, respectively; P=0.85), despite more ECVs in the acute vs the routine group ([median 3 vs 2 ECVs; P<0.05] and [≥3 ECVs in 54 vs 33% of patients, respectively; P<0.01]).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs digoxin 0.125 to 0.25 mg QD plus routine ECV Group 2: verapamil 120 to 360 mg QD with acute (within 24 hours) ECV vs verapamil 120 to 360 mg QD plus routine ECV Study medications were dosed to reach a target heart rate <100 beats/min and were administered for 4 weeks before ECV and continued during total follow-up. ECV was done one month after randomization and was only performed if anticoagulation therapy had been adequate (goal INR 2.5 to 3.5).	obtain sinus rhythm), and no contraindications to anticoagulation therapy			At the end of the 18 month follow-up period, there was not a statistically significant difference in patients with permanent AF between the verapamil and digoxin groups (28%; 95% CI, 19 to 40 vs 36%; 95% CI, 25 to 48, respectively; P=0.33), despite more ECVs in the digoxin group compared to the verapamil group ([median 3 vs 2 ECVs, respectively; P<0.001] and [≥3 ECVs in 60 vs 28% of patients, respectively; P<0.001]). Secondary: At the end of the 18 month follow-up period, there were no significant differences in QOL between the acute and the routine cardioversion groups. Also, at the end of the 18 months, there were no significant differences in QOL between the digoxin and verapamil groups.
Wyse et al.[19]	MC, RCT	N=4,060	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) AFFIRM Rhythm control therapy: amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm) vs rate control therapy: β-blockers, calcium-channel blockers, digoxin, and combinations of these drugs (doses not specified and adjusted to maintain normal sinus rhythm)	Patients 65 years and older who had AF that was likely recurrent, AF was likely to cause illness or death, long-term treatment for AF was warranted, no contraindicated to anticoagulation therapy, eligible to undergo trials of at least two drugs in both treatment strategies; and treatment with either strategy could be initiated immediately after randomization	3.5 years	Overall mortality Secondary: Composite death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest	The difference in mortality between the two groups was not significant (HR, 1.15; 95% CI, 0.99 to 1.34; P=0.08). Secondary: The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest were also similar in the two groups (P=0.33).
Van Gelder et al.[20] (2002) RACE Rhythm control	MC, RCT Patients with recurrent persistent AF or atrial flutter,	N=522 2 years	Primary: Composite of death from cardiovascular causes, heart	Primary: The composite end point occurred in 44 (17.2%) patients in rate-control group and in 60 (22.6%) patients in the rhythm-control group (absolute difference of -5.4; 90% CI, -11.0 to 0.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy: electrical cardioversion, then sotalol 160 to 320 mg (based on weight and renal function); if recurrence within 6 months, repeat electrical cardioversion, then flecainide 200 to 300 mg QD or propafenone 450 to 900 mg QD; if recurrence again, electrical cardioversion repeated along with amiodarone 600 mg QD for 4 weeks then 200 mg QD vs rate control therapy: digitalis, non-dihydropyridine calcium channel blocker, and β-blocker, alone or in combination	who have undergone one electrical cardioversion during the previous 2 years, with a maximum of 2		failure, thromboembolic complications, bleeding, the need for implantation of a pacemaker, or severe adverse effects of antiarrhythmic drugs Secondary: Not reported	Death from cardiovascular causes occurred in 18 (7.0%) patients in rate-control group and in 18 (6.8%) patients in the rhythm-control group (absolute difference of 0.2; 90% CI, -3.4 to 3.9). Heart failure occurred in nine (3.5%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of -1.0; 90% CI, -3.8 to 1.8). Thromboembolic complications occurred in 14 (5.5%) patients in rate-control group and in 21 (7.9%) patients in the rhythm-control group (absolute difference of -2.4; 90% CI, -6.0 to 1.2). Bleeding occurred in 12 (4.7%) patients in rate-control group and in nine (3.4%) patients in the rhythm-control group (absolute difference of 1.3; 90% CI, -1.5 to 4.1). Severe adverse effects of antiarrhythmic drugs occurred in two (0.8%) patients in rate-control group and in 12 (4.5%) patients in the rhythm-control group (absolute difference of -3.7; 90% CI, -6.0 to -1.4). A pacemaker was implanted in three (1.2%) patients in rate-control group and in eight (3.0%) patients in the rhythm-control group (-1.8; 90% CI, -3.9 to 0.2). Secondary: Not reported
Van Gelder et al.[21] (2010) RACE II Lenient rate control (resting	MC, NI, OL, PRO, RCT Patients ≤80 years with permanent AF for up to 12 months,	N=614 Up to 2 years of follow-up (3 years maximum)	Primary: Composite of death from cardiovascular causes, hospitalization for	Primary: Eighty one patients (38 patients receiving lenient rate control vs 43 patients receiving strict rate control) reached the primary outcome. The three year estimated cumulative incidence was 12.9 vs 14.9% receiving lenient rate control and strict rate control, with an absolute difference between lenient control and strict control of -2.0 percentage points (90% CI, -7.6 to 3.5) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
heart rate <110 bpm) vs strict rate control (resting heart rate <80 bpm and heart rate during moderate exercise <100 bpm) During the dose-adjustment phase, patients were administered one or more negative dromotropic drugs (i.e., beta-blockers, non-dihydropyridine calcium channel blockers, and digoxin), used alone or in combination and at various doses, until the heart-rate target or targets were achieved.	mean resting heart rate>80 bpm, and current use of oral anticoagulation therapy (or aspirin)		heart failure, stroke, systemic embolism, major bleeding, and arrhythmic events Secondary: Components of the primary, all-cause mortality, symptoms, functional status	a HR of 0.84 (90% CI, 0.58 to 1.21). As compared to strict rate control, lenient rate control was noninferior with regard to the prevention of the primary outcome, for both the criteria of the difference in risk (P<0.001) and the HR (P=0.001). The HR was 0.80 (90% CI, 0.55 to 1.17) after statistical adjustment for the unbalanced distribution of the presence of coronary artery disease, the use of statins, and the diastolic blood pressure. Secondary: A total of 2.9 and 3.9% of patients receiving lenient rate control and strict rate control died from cardiovascular causes (HR, 0.79; 90% CI, 0.38 to 1.65). A total of 3.8 vs 4.1% of patients were admitted for heart failure (HR, 0.97; 90% CI, 0.48 to 1.96). A total of 1.6 vs 3.9% of patients experienced a stroke (HR, 0.35; 90% CI, 0.13 to 0.92). A total of 5.3 vs 4.5% of patients experienced major bleeding (HR, 1.12; 90% CI, 0.60 to 2.08). All-cause mortality occurred in 17 patients receiving lenient rate control (5.6% at three years) compared to 18 patients receiving strict rate control (6.6% at three years; HR, 0.91; 90% CI, 0.52 to 1.59). Death from noncardiovascular causes occurred in eight and seven patients receiving lenient and strict rate control. At the end of the follow-up period, 129/283 (45.6%) and 126/274 (46.0%) of patients receiving lenient and strict rate control had symptoms associated with AF (P=0.92); dyspnea (30.0 vs 29.6%; P=0.90), fatigue (24.4 vs 22.6%; P=0.63), and palpitations (10.6 vs 9.5%; P=0.66). At the end of follow-up period, in the lenient rate control group and in the strict control group, 70.0 and 70.4% of patients, respectively, were in NYHA functional class I, 23.3 vs 23.4% were in class II, and 6.7 vs 6.2% were in class II (P=0.74 for all comparisons).
Groenveld et al.[22] (2011) RACE II Lenient rate control (resting heart rate <110 bpm)	Post-hoc analysis of RACE II Patients ≤80 years with permanent AF for up to 12 months, mean resting heart rate>80 bpm, and current use of oral	N=614 Up to 2 years of follow-up (3 years maximum)	Primary: QOL (SF-36), AF severity scores (MFI-20) Secondary: Not reported	Primary: At the end of follow-up all SF-36 subscales were comparable between patients receiving lenient and strict rate control. At baseline and at the end of the trial there were no differences in the MFI-20 subscales between patients receiving lenient and strict rate control. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs strict rate control (resting heart rate <80 bpm and heart rate during moderate exercise <100 bpm) During the dose-adjustment phase, patients were administered one or more negative dromotropic drugs (i.e., beta-blockers, non-dihydropyridine calcium channel blockers, and digoxin), used alone or in combination and at various doses, until the heart-rate target or targets were achieved.	anticoagulation therapy (or aspirin)			
Opolski et al.[23] (2004) HOT CAFÉ Rhythm control therapy: propafenone 450 to 600 mg QD, disopyramide 300 to 600 mg QD, or sotalol 160 to 320 mg QD	MC, OL, RCT Patients between 50 to 75 years of age with AF known to be present continuously for between seven days and two years with acceptable etiology of the arrhythmia	N=205 1 year	Primary: Composite of death from any cause (thromboembolic complications and intracranial or other major hemorrhage) Secondary: Rate control, sinus rhythm	Primary: There was not a significant difference in composite of death from any cause between the rate control group and the rhythm control group (OR, 1.98; 95% CI, 0.28 to 22.3; P>0.71). Secondary: The patients in the rhythm control group had a significantly lower mean heart rate (79.1±8.6 beats/min) in 24-hour Holter monitoring compared to the patients in the rate control group (85.8±7.5 beats/min; P<0.003). Four patients in the rhythm control group experienced proarrhythmic effects. Whether this lead to discontinuation of therapy was not mentioned.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rate control therapy: β-blockers, non-dihydropyridine calcium channel blockers, digoxin, or a combination of these drugs. All patients underwent electric cardioversion prior to the initiation of study medication.	related to ischemic heart disease, arterial hypertension, hemodynamically insignificant valvular heart disease, or lack of assessable etiology		maintenance, discontinuation of therapy (proarrhythmic effects), hemorrhage, hospitalization, new or worsening CHF, or changes in exercise tolerance	At the end of the study, 66 patients (63.5%) in the rhythm control arm were in sinus rhythm, with 27 of these patients successfully maintained with the first antiarrhythmic compound administered after the first cardioversion. There was not a statistical difference seen in bleeding complications between the rhythm control group (eight patients) and rate control group (five patients). A significantly lower number of hospitalizations were seen in the rate control arm compared to the rhythm control arm (12 vs 74%, respectively; P<0.001). Both the rhythm control group and rate control group had significant improvements in CHF class at some point during follow-up compared to baseline (P<0.001 and P<0.05, respectively). No difference in NYHA functional class between patients initially randomized to the two strategies was found at the end of the follow-up period. At the end of the study, both maximal workload and exercise duration were higher in the rhythm control arm compared to the rate control arm (P<0.001 and P<0.001, respectively).
Lafuente-Lafuente et al.[24] (2009) Antiarrhythmic drugs (amiodarone, aprindine, azimilide, bidisomide, flecainide, disopyramide, dofetilide, dronedarone, quinidine, propafenone, sotalol)	MA (45 trials) Adults >16 years of age who had AF of any type and duration and in whom sinus rhythm had been restored, spontaneously or by any therapeutic intervention	N=12,559 Variable duration	Primary: Mortality, embolic complications, adverse events Secondary: Use of anticoagulation, recurrence of AF	Primary: No deaths were reported with flecainide in the three trials. Quinidine showed a trend to increase mortality compared to controls (OR, 2.26; 95% CI, 0.93 to 5.45; P=0.07). This trend was significant if missing patients were counted as deaths (OR, 2.29; 95% CI, 1.05 to 5.01; P=0.04), and when class IA drugs (quinidine and disopyramide) were combined (OR, 2.39; 95% CI 1.03 to 5.59; P=0.04). The number NNH for class IA drugs was 109 patients treated for one year to have one excess death. Sotalol showed a trend to increased mortality (OR, 2.09; 95% CI, 0.97 to 4.49; P=0.06) compared to controls. This trend was significant if missing patients were counted as deaths (OR, 2.27; 95% CI, 1.36 to 3.77; P=0.002). Amiodarone was associated with a reduction in mortality compared to combined class I drugs (OR, 0.39; 95% CI, 0.19 to 0.79; NNT 17). When compared to controls, amiodarone showed no significant difference in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo, drugs for rate control (digoxin, calcium channel blockers, β-blockers) or no treatment				mortality. No other significant difference in mortality was detected, either vs control or between different antiarrhythmics. The analysis of cardiovascular mortality gave the same results as that of all-cause mortality. Only five of the 30 studies comparing antiarrhythmics with a control reported stroke outcomes. They reported six strokes in 650 patients in the control groups and 20 strokes in 1,755 patients treated with antiarrhythmics. Withdrawals due to adverse effects were more frequent with all drugs, except aprindine and dofetilide, compared to controls. Pooled events rates varied from 9 to 23% for withdrawals due to adverse effects. The mean number of patients needed to treat for one year to have one excess withdrawal from treatment ranged from nine (quinidine) to 27 (amiodarone, propafenone, or sotalol). Quinidine caused more withdrawals than the other class I drugs (OR, 2.25; 95% CI 1.45 to 3.51; P=0.0003). Amiodarone produced significantly fewer withdrawals than other class I drugs combined (OR, 0.52; 95% CI, 0.34 to 0.81; P=0.004). All antiarrhythmics increased proarrhythmic effects, with the exception of amiodarone and propafenone. Pooled events rates varied from 1 to 7% for proarrhythmia. The NNH for proarrhythmia ranged between 17 (flecainide) and 119 (dofetilide). Amiodarone produced significantly less proarrhythmic events than other class I drugs combined (OR, 0.28; 95% CI, 0.13 to 0.59; P=0.0007). Secondary: All class IA, class IC and class III drugs significantly reduced the recurrence of atrial fibrillation. Pooled recurrence rates of atrial fibrillation at 1 year were 71 to 84% in controls and were reduced to 42% to 67% in patients treated with antiarrhythmics. The NNT for one year to avoid one recurrence of atrial fibrillation were three with amiodarone, four with flecainide, five with dofetilide and propafenone, eight with quinidine and sotalol and 10 with dronedarone. Amiodarone reduced recurrences of AF significantly more than combined class I drugs (OR, 0.31; 95% CI, 0.21 to 0.45; P<0.0001) and more than sotalol (OR, 0.43; 95% CI 0.29 to 0.64; P<0.0001). No other differences between antiarrhythmics were detected.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Chronic anticoagulation with warfarin was mandatory in only three studies. The decision on anticoagulation was left to the judgment of the attending physician in the remaining studies.
Heart Failure				
Koh, Kwan et al.[25] (1995) Without digoxin, diltiazem, or betaxolol (Group I) vs digoxin 0.125 to 0.5 mg QD (Group II) vs digoxin 0.125 to 0.5 mg QD and diltiazem 90 mg BID (Group III) vs digoxin 0.125 to 0.5 mg QD and betaxolol 20 mg QD (Group IV)	PRO, RCT Patients with chronic heart failure for >1 month	N=45 4 weeks	Primary: Heart rate, BP, rate-pressure Secondary: Not reported	Primary: Resting ventricular rates were lower in all patients receiving active treatment (groups II, III, IV) compared those patients in group I who did not receive digoxin (P<0.01). Ventricular rates during exercise were lower in groups III and IV compared to groups I and II (P<0.01). No significant differences in ventricular rate were noted between groups III and IV, either at rest or during exercise (P<0.01). SBP was not significantly different between the four groups (P=0.09). Rate-pressure product at rest and during exercise was significantly lower in groups III and IV compared to groups I and II (P<0.01). Secondary: Not reported
DIG[26] (1997) Digoxin 0.125 to 0.5 mg QD vs	DB, MC, PC, RCT Patients ≥21 years old with heart failure and LVEF ≤45% who were in normal sinus rhythm	N=6,800 37 months	Primary: Mortality Secondary: Mortality from cardiovascular causes, death from worsening heart	Primary: In the digoxin group, there were 1,181 (34.8%) deaths compared to 1,194 (35.1%) deaths in patients receiving placebo (95% CI, 0.91 to 1.07; P=0.80). Secondary: In the digoxin group, 1,016 (29.9%) patients died from cardiovascular compared to 1,004 (29.5%) patient deaths in the placebo group (95% CI, 0.93 to 1.10; P=0.78).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Patients continued on their other CHF therapies (including diuretics and ACE inhibitor). Initial dosing of digoxin was based on patient's age, sex, weight and renal function.			failure, hospitalization for worsening heart failure, and hospitalization for other causes (specifically due to digoxin toxicity)	There were 394 deaths in the digoxin group that were attributed to worsening heart failure compared to 449 deaths in the placebo (95% CI, 0.77 to 1.01; P=0.06). In the digoxin group, 910 patients were hospitalized for worsening heart failure compared to 1,180 patients in the placebo group (95% CI, 0.66 to 0.79; P<0.001). Overall, the placebo group had a significantly higher number of patients hospitalized compared to the digoxin group, 2,184 vs 2,282 respectively (95% CI, 0.87 to 0.98; P<0.006). Other reasons for hospitalizations included cardiac events and respiratory infection. There was a statistically significantly higher number of patients in the digoxin group hospitalized for suspected digoxin toxicity compared to placebo, 67 vs 31, respectively (95% CI, 1.42 to 3.32; P<0.001).
Ather et al.[27] (2011) DIG Digoxin 0.125 to 0.5 mg QD vs placebo	Post-hoc analysis of DIG Patients ≥21 years old with heart failure and LVEF ≤45% who were in normal sinus rhythm; the DIG database was partitioned into 20 clusters	N=6,800 37 months	Primary: Multivariate Cox regression analyses were used to identify clusters in which digoxin is associated with either an increase ($Mortality_{dig}HR>1$), decrease ($Mortality_{dig}HR<1$), or no association with all-cause mortality ($Mortality_{dig}HR$-NS); and separately, with an increase ($HFA_{dig}HR>1$), decrease ($HFA_{dig}HR<1$), or no association with	Primary: Nine hundred and thirty eight patients were identified in the $Mortality_{dig}HR>1$ group, 6,818 patients in the $Mortality_{dig}HR$-NS group, and non in the $Mortality_{dig}HR<1$. The $Mortality_{dig}HR>1$ group had a higher prevalence of females, diabetes, hypertension, higher age, SBP, heart rate, and ejection fraction compared to the $Mortality_{dig}HR$-NS group. Six thousand three hundred and twenty five patients were identified in the $HFA_{dig}HR<1$ group, 1,431 patients in the $HFA_{dig}HR$-NS group, and none in the $HFA_{dig}HR>1$ group. The $HFA_{dig}HR$-NS group had a higher prevalence of females and hypertension, higher SBP, body mass index, and ejection fraction; and lower prevalence of peripheral edema and third heart sound compared to the $HFA_{dig}HR<1$ group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			heart failure admissions (HFA_{dig}HR-NS) Secondary: Not reported	
Meyer et al.[28] (2008) DIG Digoxin 0.125 to 0.5mg QD vs placebo The majority of patients enrolled were also receiving diuretics and ACE inhibitors	Subgroup analysis of DIG trial (comparing equal numbers of patients with systolic [n=916] and diastolic heart failure [916]) Patients ≥21 years old with chronic heart failure and LVEF ≤45% who were in normal sinus rhythm	N=1,832 2 to 3.2 years	Primary: Heart failure hospitalization or heart failure mortality (combined and separately) at the end of 3.2 years and 2 years of follow-up Secondary: Not reported	Primary: After 3.2 years of median follow-up, the combined end point of heart failure hospitalization or heart failure mortality occurred in 28 and 32% of patients with systolic heart failure (HR, 0.85; 95% CI, 0.67 to 1.08, P=0.188) and in 20 and 25% of patients with diastolic heart failure (HR, 0.79; 95% CI, 0.60 to 1.03; P=0.085) who were receiving digoxin and placebo, respectively. After 3.2 years of median follow-up, the effect of digoxin on heart failure hospitalization was similar in patients with systolic heart failure (HR, 0.80; 95% CI, 0.62 to 1.03, P=0.079) and diastolic heart failure (HR, 0.77; 95% CI, 0.57 to 1.03, P=0.074). At the end of two years of follow-up, the effect of digoxin on the combined end point was similar in patients with systolic heart failure (HR, 0.72; 95% CI, 0.55 to 0.95; P=0.022) and those with diastolic heart failure (HR, 0.69; 95% CI, 0.50 to 0.95; P=0.025). At the end of two years of follow-up, digoxin decreased heart failure hospitalization for systolic heart failure (HR, 0.73; 95% CI, 0.54 to 0.97; P=0.033) and diastolic heart failure (HR, 0.64; 95% CI, 0.45 to 0.90; P=0.010). Secondary: Not reported
Ahmed, Rich, Love et al.[29] (2006) DIG Digoxin 0.125 to 0.5 mg QD vs	Posthoc analysis of DIG Patients with heart failure, regardless of ejection fraction, and who were in normal SR	N=5,548 40 months	Primary: All-cause mortality Secondary: Mortality due to cardiovascular causes and heart failure, hospitalizations	Primary: At 40 months, all cause death rate was 33% in the placebo group, 29% in the group of patients with a SDC of 0.5 to 0.9 ng/mL, and 42% in the group of patients with the SDC of ≥1.0 ng/mL (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.77; 95% CI, 0.67 to 0.89; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 1.06; 95% CI, 0.93 to 1.20; P=0.406). Secondary: At 40 months, cardiovascular mortality rate was 26% in the placebo group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo QD Patients continued on their other CHF therapies (including diuretics and ACE inhibitors) Initial dosing of digoxin was based on patient's age, sex, weight and renal function.			due to all causes, cardiovascular causes, and worsening heart failure	24% in the SDC of 0.5 to 0.9 ng/mL group, and 33% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.83; 95% CI, 0.71 to 0.97; P=0.019 and placebo vs SDC ≥1 ng/mL; adjusted HR, 1.07; 95% CI, 0.93 to 1.24; P=0.339). At 40 months, mortality rate due to heart failure was 12% in the placebo group, 9% in the SDC of 0.5 to 0.9 ng/mL group, and 14% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.63; 95% CI, 0.49 to 0.82; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.87; 95% CI, 0.70 to 1.09; P=0.236). At 40 months, all cause hospitalization rates were 67% in the placebo group, 64% in the SDC of 0.5 to 0.9 ng/mL group, and 71% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.85; 95% CI, 0.78 to 0.92; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.95; 95% CI, 0.87 to 1.05; P=0.331). At 40 months, cardiovascular hospitalization rates were 53% in the placebo group, 48% in the SDC of 0.5 to 0.9 ng/mL group, and 55% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.79; 95% CI, 0.72 to 0.88; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.91; 95% CI, 0.82 to 1.01; P=0.086). At 40 months, hospitalization rates due to heart failure were 33% in the placebo group, 23% in the SDC of 0.5 to 0.9 ng/mL group, and 29% in the SDC of ≥1.0 ng/mL group (placebo vs SDC 0.5 to 0.9 ng/mL; adjusted HR, 0.62; 95% CI, 0.54 to 0.72; P<0.0001 and placebo vs SDC ≥1 ng/mL; adjusted HR, 0.68; 95% CI, 0.59 to 0.79; P=0.086).
Ahmed et al.[30] (2006) Digoxin 0.125 to 0.5 mg QD vs placebo Patients continued	MC, PC, RCT Patients with diastolic heart failure (LVEF >45%) and normal SR at baseline This was an ancillary trial conducted in	N=988 37 months	Primary: Combined end point of heart failure hospitalization or heart failure mortality Secondary: Not prespecified, however the	Primary: At the end of the study, there was not a statistically significant difference in the number of patients who experienced heart failure hospitalization or heart failure mortality between the digoxin group and the placebo group (102 [21%] vs 119 [24%], respectively; HR, 0.82; 95% CI, 0.63 to 1.07; P=0.136). Secondary: At the end of the study, there was not a statistically significant difference in the number of all-cause deaths between the digoxin group and the placebo group (115 [23%] vs 116 [23%], respectively; HR, 0.99; 95% CI, 0.76 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
on their other CHF therapies (including diuretics and ACE inhibitor). Initial dosing of digoxin was based on patient's age, sex, weight and renal function.	parallel with the main DIG trial.[22]		following outcomes were studied: all-cause and cardiovascular mortality, all-cause and cardiovascular hospitalizations, and the combined outcome of heart failure hospitalization and cardiovascular mortality	1.28; P=0.925). Also, the difference in the number of cardiovascular deaths was not significantly different between the digoxin and the placebo group (81 patients in each group; HR, 1.00; 95% CI, 0.73 to 1.36; P=0.978). At the end of the study, there was not a statistically significant difference in the number of all-cause hospitalizations between the digoxin group and the placebo group (68% vs 67%, respectively; HR, 1.03; 95% CI, 0.89 to 1.20; P=0.683). Also, the difference in the number of cardiovascular hospitalizations was not significantly different between the digoxin and the placebo group (241 [49%] vs 225 [45%], respectively; HR, 1.10; 95% CI, 0.92 to 1.32; P=0.301). At the end of the study, there was not a statistically significant difference in the number of patients who experienced heart failure hospitalization or cardiovascular mortality between the digoxin group and the placebo group (142 [29%] vs 154 [31%], respectively; HR, 0.88; 95% CI, 0.70 to 1.11; P=0.269).
Uretsky et al.[31] (1993) PROVED Digoxin 0.125, 0.25, 0.375, or 0.5 mg QD vs placebo QD Digoxin was dosed to obtain a serum digoxin concentration of 0.9 to 2.0 ng/mL Patients continued on background therapy of diuretics.	DB, MC, PC, PG, RCT Patients ≥18 years old with NYHA Class II or III heart failure, normal sinus rhythm, receiving digoxin and diuretics, LVEF ≤35%, a LVED dimension of ≥60 mm or 34 mm/m^2	N=88 12 weeks	Primary: Treadmill time on maximal exercise testing, distance covered in a 6-minute walking test, incidence of treatment failure, time to treatment failure Secondary: Change in signs and symptoms of heart failure, MLHF questionnaire, heart failure score, 7-point GEP, LVEF, vital signs, body weight	Primary: At 12 weeks, patients in the placebo group experienced a median decline of 96 seconds in maximal exercise testing compared to a 4.5 second increase in the digoxin group (P=0.003). Digoxin did not display a significantly different effect on distance covered in a 6-minute walking test. Patients in the placebo group experienced a 39% rate of treatment failures compared to 19% in the digoxin group (P=0.039). The patients in the placebo group also experienced a decreased time to treatment failure compared to the digoxin group (P=0.037). Treatment failures included hospital admissions, increase in drug therapy and death. Secondary: At the end of the 12-week study, there was not a statistically significant difference between the placebo and digoxin groups in changes in signs and symptoms of heart failure, MLHF questionnaire or heart failure score. At the end of 12 weeks, patients in the digoxin group experienced a mean increase in LVEF by 2±2% compared to a mean decrease in LVEF of 3±2% for the patients in the placebo group (P=0.016).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Heart rate and body weight were significantly lower in the digoxin group compared to the patients in the placebo group (P=0.03 and P=0.044, respectively).
Packer et al.[32] (1993) Digoxin QD vs placebo QD All patients started in an 8 week, single-blind run-in period during which the doses of background therapy for heart failure were adjusted to achieve optimal clinical benefits. After the run-in period, patients were randomized to either continue receiving digoxin therapy or receive placebo. Digoxin was dosed to obtain a serum digoxin concentration of 0.9 to 2.0 ng/mL Patients continued on background	DB, MC, PC, RCT Patients ≥18 years old with NYHA Class II or III heart failure, LVEF ≤35%, a LVED dimension of ≥60 mm or 34 mm/m^2, evidence of reduced exercise capacity, and normal sinus rhythm, who were clinically stable while receiving digoxin, diuretics, and an ACE inhibitor	N=178 12 weeks	Primary: Rates of withdrawal from the study due to worsening heart failure, time to withdrawal, changes in exercise tolerance Secondary: Effects of discontinuing digoxin therapy on symptoms, QOL, functional class, overall progress during the study and cardiac dimensions and function	Primary: Four patients who received digoxin, compared to 23 patients in the placebo group, withdrew from the study due to worsening of heart failure (P<0.001). The patients in the placebo group had a higher risk of worsening heart failure compared to the patients in the digoxin group over the 12 week study (RR, 5.9; 95% CI, 2.1 to 17.2; P<0.001). Exercise tolerance remained stable in patients receiving digoxin compared to deterioration in exercise tolerance in patients receiving placebo. The median difference in exercise duration between the two groups after 12 weeks was 42 seconds (P=0.006). Exercise endurance remained constant in patients receiving digoxin compared to a decrease in patients receiving placebo. The median difference in submaximal exercise endurance between the two groups after 10 weeks was 41 meters (P=0.01). Secondary: Of the patients in the placebo group, 38% experienced worsening dyspnea and fatigue compared to 16 and 18% of patients in the digoxin group (P=0.14 and P=0.04, respectively). Thirty-three percent of patients in the placebo group experienced a less of an improved quality of life compared to 47% in the digoxin group (P=0.04). Also, 48% of patients in the placebo group experienced a more frequent decline in quality of life compared to 41% in the digoxin group (P=0.04). In the placebo group, 27% of patients were reported as having a deterioration in NYHA class compared to 10% of patients in the digoxin group (P=0.019). Thirty-one percent of patients in the placebo group reported that they felt moderately worse or much worse, compared to 9% of patients in the digoxin group (P=0.007).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
therapy of diuretics and an ACE inhibitor.				
Dhaliwal et al.[33] (2008) Digoxin, renin-angiotensin inhibition and beta-blockade vs renin-angiotensin inhibition and beta-blockade	RETRO Patients with a diagnosis of congestive heart failure with depressed LVEF (≤45%) and who were on a regimen of rennin-angiotensin inhibitor(s) and beta-blocker(s) with or without digoxin	N=347 26 months	Primary: Combined and individual rates of heart failure-related hospitalizations and total mortality Secondary: Not reported	Primary: In the adjusted analysis, heart failure hospitalizations (HR, 1.08; 95% CI, 0.77 to 1.50; P=0.66), total mortality (HR, 1.03; 95% CI, 0.78 to 1.35, P=0.85), and the combined end point of heart failure hospitalization and total mortality (HR, 1.11; 95% CI 0.81 to 1.53, P=0.52) were similar between individuals who had digoxin as part of their drug regimen and those who did not. In unadjusted analyses, digoxin use was associated with a nonsignificant increase in heart failure hospitalization rates. The combined endpoint of heart failure hospitalization and total mortality and individual end points were not different between patients on digoxin therapy and those not on digoxin therapy in any of the prespecified analyses according to subgroups of ejection fraction (≤25 vs >25%), NYHA class (III or IV vs I or II), use vs nonuse of β-blockers, presence or absence of atrial fibrillation, and admission or discharge heart rates of ≤60 or ≥60 beats/minute. Secondary: Not reported
Fauchier et al.[34] (2009) Digoxin vs beta-blockers vs digoxin plus beta-blockers vs No digoxin or	RETRO Patients with primary or secondary diagnosis of both AF and heart failure between January 2000 and January 2004 were retroactively identified and followed until September 2007	N=1,269 881 days	Primary: All cause mortality Secondary: Not reported	Primary: Compared to the control group (no β-blocker or digoxin), treatment with a β-blocker (RR, 0.58; P=0.005) or digoxin plus beta-blockers (RR, 0.59; P=0.008) was associated with a lower risk of death. Treatment with digoxin alone was not associated with a better survival. There was a similar reduction in mortality when considered separately: heart failure patients with atrial fibrillation, association or not with coronary artery disease, and heart failure with decreased or preserved systolic function. The initial multivariate model was constructed using the predictors of all cause mortality as potential confounders. After adjustment, treatment with β-blocker alone or in combination with digoxin remained significantly associated with a better survival (RR, 0.618; P=0.04 and RR, 0.543; P=0.01, respectively). A stepwise selection technique was used to determine the final model, which included four factors associated with mortality: older age (P<0.001),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
beta-blockers (control group)				decreased left ventricular ejection fraction (P=0.001), chronic renal insufficiency (P=0.007), and lack of treatment with beta-blockers alone or in combination with digoxin was associated with better survival (RR, 0.618; P=0.04 and RR, 0.543; P=0.01). Secondary: Not reported
Friberg et al.[35] (2009) Digoxin vs no digoxin	COHORT, OB Individuals treated as inpatients or outpatients for AF or atrial flutter	N=2,824 4.6 years (mean duration)	Primary: Mortality Secondary: Rates of hospitalization for heart failure, number of days at hospital for any cause, frequency of MI, frequency of ischemic stroke, and rate of pacemaker implantations	Primary: In the unadjusted analysis, 1,038 patients died; 412 were prescribed digoxin at index and 626 did not receive digoxin. The mortality rate was higher among individuals who were treated with digoxin (51 vs 31%; P<0.001; HR, 1.94; 95% CI, 1.71 to 2.20). When adjusted for age, gender, comorbidities and medications, the difference in mortality was not significant (HR, 1.10; 95% CI, 0.94 to 1.28). The relationship between mortality and digoxin treatment at the latest, rather than the first, contact during the observation period was also studied. Unadjusted mortality was higher among patients treated with digoxin (48 vs 31%, P<0.001); However, after multivariable adjustment, there was no difference (HR, 1.05; 95% CI, 0.92 to 1.20). When patients were matched according to their individual propensity scores, there was no difference in mortality related to digoxin use (HR, 1.05; 95% CI, 0.90 to 1.23). Secondary: Individuals treated with digoxin, who had high propensity scores for this treatment, were less often hospitalized for heart failure. The number of days in the hospital for any cause did not differ between groups. There was no difference in the frequency of myocardial infarctions or ischemic strokes related to digoxin use. There was an increased rate of pacemaker implantations among patients with digoxin as compared to those without digoxin (HR, 1.99; 95% CI, 1.16 to 3.43).
Georgiopoulou et al.[36] (2009)	COHORT, RETRO Patients 18 to 70	N=455 27 months	Primary: Time to death, urgent	Primary: Death, urgent transplantation, or left ventricular assist device implantation occurred in 36.6% of patients on digoxin compared to 15.8% of patients not

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Digoxin (median daily dose of 0.13mg/day) vs no digoxin	years of age with advanced heart failure, LVEF ≤30% on maximum tolerated medical therapy, and NYHA Class II to IV	(median duration)	transplantation, or left ventricular assist device implantation Secondary: Composite of the primary outcome plus hospitalization for heart failure, all-cause hospitalizations, and heart failure-related hospitalizations	receiving digoxin (HR, 2.28; 95% CI, 1.51 to 3.43; P<0.001). Secondary: The composite of primary outcome plus heart failure hospitalization occurred in 63.0% of patients on digoxin compared to 40.4% of patients not receiving digoxin (HR, 1.71; 95% CI, 1.32 to 2.23; P<0.001). All-cause hospitalization rates (HR, 1.58; 95% CI, 1.18 to 2.13; P<0.01) and heart failure-related hospitalization rates (HR, 1.81; 95% CI, 1.17 to 2.80; P<0.05) were higher in patients taking digoxin compared to those who were not taking digoxin.
Butler et al.[37] (2010) Val-HeFT Digoxin vs no digoxin The analyses of this trial were carried out in patient groups based on digoxin use at baseline.	Post-hoc analysis of Val-HeFT (DB, PC, MC, RCT) Patients with symptomatic heart failure	N=5,010 (n=3,374 digoxin-treated patients, n=1,636 patients not receiving digoxin) 23 months (mean duration)	Primary: All-cause mortality, first morbid event, heart failure hospitalizations Secondary: Not reported	Primary: Risk of death (n=3,249; HR, 1.28; 95% CI, 1.05 to 1.57; P=0.02), first morbid event (n=3,249; HR, 1.35; 95% CI, 1.15 to 1.59; P<0.001), first hospitalization for heart failure (n=3,249; HR, 1.41; 95% CI, 1.12 to 1.78; P=0.004), and sudden deaths (n=3,067; HR, 1.36; 95% CI, 1.04 to 1.78; P=0.03), but not pump failure deaths (n=2,875; HR, 1.48; 95% CI, 0.95 to 2.30; P=0.08), remained were significantly higher among patients receiving baseline digoxin compared to those were not. Secondary: Not reported
Siu et al.[38] (2009) Digoxin IV 0.5 mg bolus dose, followed by 0.25 mg every 8 hours	OL, RCT Patients who presented to the Emergency Department with symptomatic acute AF for <48 hours	N=150 3 years	Primary: Sustained ventricular rate control (<90 bpm) within 24 hours Secondary: Time to ventricular	Primary: After the initial 24 hours, ventricular rate control was achieved in 119 of 150 patients (79%). Secondary: The median time to ventricular rate control in patients assigned to the diltiazem regimen was three hours (range: 1 to 21 hours) and was noticeably shorter than that of digoxin (six hours, 3 to 15 hours) and amiodarone (seven

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs diltiazem IV 0.25 mg/kg bolus injection over 2 minutes, followed by a second bolus of 0.35 mg/kg if ventricular rate remained >90 bpm 15 minutes later, and then a maintenance infusion at 10 mg/hr for 24 hours vs amiodarone IV loading infusion of 300 mg over the first hour, followed by 10 mg/kg over 24 hours	and rapid ventricular rate >120 bpm requiring hospitalization		rate control, sinus rhythm conversion, symptom severity, hospital stay, and adverse drug events	hours, 1 to 18 hours) based on the log-rank test (P<0.0001). Among the patients, 45 assigned to diltiazem achieved ventricular rate control (90%), which was significantly more than among those assigned to digoxin (74%; P=0.047) and amiodarone (74%; P=0.047). Patients assigned to diltiazem had persistently the lowest mean ventricular rate after the first hour of drug administration compared to the other two groups (P<0.05). Sinus rhythm conversion rate was 31% within the first 24 hours and 38% upon discharge. There was no significant difference in sinus rhythm conversion rate among the diltiazem regimen, digoxin regimen, and amiodarone regimen within the first 24 hours (34 vs 24 vs 36%; P>0.05) and on discharge (42 vs 28 vs 44%; P>0.05). There were no differences among the three groups in the median time to sinus conversion: five hours (1 to 16 hours), six hours (1 to 19 hours), and seven hours (1 to 17 hours), respectively (P>0.05). Patients receiving diltiazem had lower AF symptom severity scores at 24 hours compared to digoxin (P=0.047) and amiodarone (P=0.01). There was no significant difference in AF symptom frequency scores at 24 hours among the three groups. At 24 hours, patients receiving diltiazem had the greatest reduction in both AF symptom frequency score (12.7; P=0.001) and severity score (9.8; P<0.0001) compared to those who received digoxin (8.6 and 6.1) or amiodarone (9.0 and 6.1). Patients who achieved spontaneous sinus conversion had the greatest reduction in AF symptom frequency score and severity score (17.2 and 11.0, respectively) compared to those who achieved ventricular rate control (9.4 and 7.7) or failed ventricular rate control (1.2 and 0.1; all, P<0.001). Among patients who remained in AF, those receiving diltiazem had the greatest reduction in both AF symptom frequency score (9.0) and severity score (7.8) in comparison with patients receiving digoxin (6.3 and 5.3; P=0.049), and patients receiving amiodarone (5.6 and 3.3; P<0.01). The mean hospital stay was 4.4 days. There was a significantly shorter hospital stay (P=0.023) in the diltiazem group (3.9 days) compared to the digoxin (4.7 days) and amiodarone groups (4.7 days).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Only one patient who received amiodarone demonstrated a major adverse event with phlebitis at the intravenous access site requiring prolonged hospitalization. No bradycardia, hypotension, new-onset CHF, or MI was observed in any of the patients.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, NI=noninferiority, OB=observational, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, XO=cross-over
Miscellaneous abbreviations: ACE inhibitor=angiotensin-converting enzyme inhibitor, AF=atrial fibrillation, AMI=acute myocardial infarction, BP=blood pressure, CHF=congestive heart failure, CI=confidence interval, ECG=electrocardiogram, ECV=electrical cardioversions, HR=heart rate, INR=international normalized ratio, LVED=left ventricular end-diastolic, LVEF=left ventricular ejection fraction, MET=mean exercise tolerance, MFI-20=Multidimensional Fatigue Inventory-20, MI=myocardial infarction, MLHF=Minnesota Living with Heart Failure, NNH=number needed to harm, NNT=number needed to treat, NYHA=New York Heart Association, OR=odds ratio, QOL=quality of life, RR=relative risk, SBP=systolic blood pressure, SDC=serum digoxin concentration, SF-36=Short Form Health Survey

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Cardiotonic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Digoxin	injection, solution, tablet	Lanoxin®*, Lanoxin Pediatric®	$	$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Digoxin is the only cardiotonic agent that is currently available. It is an effective treatment option for heart failure due to its positive inotropic and neurohormonal deactivating effects. It is also beneficial for atrial arrhythmias due to its vagomimetic actions. Digoxin injection, solution, and tablets are all available in a generic formulation. Although there are minor differences with respect to pharmacokinetic parameters, all digoxin products are equally effective. Due to its potential for drug interactions and other toxicities, digoxin therapy should be monitored closely.[1-3,14]

There are several guidelines that discuss the role of digoxin for the treatment of atrial fibrillation and heart failure. Digoxin slows atrioventricular conduction more effectively at rest than during exercise, but does not block exercise-induced tachycardia, which limits its use. For the treatment of atrial fibrillation, β-blockers and nondihydropyridine calcium channel antagonists are recommended as initial therapy to control heart rate.[4,9] Digoxin can effectively control heart rate at rest and is indicated for patients with heart failure, left ventricular dysfunction and for sedentary individuals.[4] A combination of digoxin and either a β-blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise.[4,9] Digoxin should not be used for the pharmacologic cardioversion of atrial fibrillation. It has not been proven to be effective in preventing postoperative atrial fibrillation and is not recommended in this setting.[5,6] For the treatment of heart failure, angiotensin converting enzyme inhibitors, β-blockers, and diuretics are the cornerstone of therapy. Digoxin may be considered for patients with systolic dysfunction who have signs/symptoms of heart failure while receiving standard therapy. It has been shown to improve symptoms, exercise tolerance, quality of life and decrease hospitalizations for heart failure; however, it has no effect on survival. Digoxin is not useful for the acute management of decompensated heart failure.[8-11] The available guidelines do not give preference to one particular digoxin formulation over another.[4-13]

Therefore, all brand cardiotonic agents within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand cardiotonic agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Pharmacotherapy Review of Cardiac Drugs, Miscellaneous
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I. Overview

Angina occurs when myocardial oxygen demand exceeds supply, which results in chest discomfort or pain. Common treatments for chronic angina include nitrates, β-blockers, and calcium channel blockers. Nitrates reduce oxygen demand by decreasing left ventricular pressure and systemic vascular resistance, as well as by dilating coronary arteries. β-blockers reduce heart rate and contractility by competitively blocking the response to beta-adrenergic stimulation in the heart. Calcium channel blockers increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction and reducing contractility. They also decrease oxygen demand by reducing systemic vascular resistance and arterial pressure.[1]

Ranolazine is the only miscellaneous cardiac drug that is currently available and it is approved for the treatment of chronic angina. It may be used in combination with β-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid lowering therapy, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers. The exact mechanism of ranolazine is unknown. The anti-ischemic and antianginal effects do not depend upon reductions in heart rate or blood pressure.[2]

The miscellaneous cardiac drugs that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ranolazine is not available in a generic formulation. This class was last reviewed in August 2010.

Table 1. Cardiac Drugs, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ranolazine	extended-release tablet	Ranexa®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous cardiac drugs are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cardiac Drugs, Miscellaneous

Clinical Guideline	Recommendations
Institute for Clinical Systems Improvement: **Stable Coronary Artery Disease[3] (2011)**	• The use of one aspirin tablet daily (81 to 162 mg) is strongly recommended unless there are medical contraindications. • In patients with mild, stable coronary artery disease (CAD), drug therapy may be limited to short-acting sublingual nitrates on an as-needed basis. • β-blockers should be used in all status post-myocardial infarction (MI) patients, based on studies showing mortality reduction. • β-blockers are the preferred first-line therapy for reducing symptoms of angina in patients with stable CAD. • Drugs with intrinsic sympathomimetic activity should be avoided. • Abrupt withdrawal of all β-blockers should be avoided. • If β-blockers cannot be prescribed as first-line therapy, nitrates are the preferred alternative first-line therapy because of efficacy, low cost, and relatively few adverse events. • For patients who are unable to take β-blockers or long-acting nitrates, the use of calcium channel blockers has been shown to be clinically

Clinical Guideline	Recommendations
	effective in decreasing symptoms of angina. Dihydropyridines as monotherapy may exacerbate angina. • Combination therapy may be necessary in selected patients, but it increases adverse events and medical costs. A combination of β-blockers and long-acting nitrates is preferred because of cost, efficacy, and reduced potential for adverse events. • If after several attempts at adjusting the medications, a therapeutic combination is not achieved for the patient, a cardiology consultation or referral may be appropriate. • Among patients with stable angina, angiotensin converting enzyme (ACE) inhibitors are most beneficial to patients with left ventricular dysfunction post-MI, persistent hypertension, and diabetes. If the patient cannot tolerate ACE inhibitors, a potential substitute would be an angiotensin II receptor blocker (ARB). • The decision to initiate daily drug therapy for CAD is based upon the symptom complex of the patient in combination with findings from the history, physical examination, laboratory studies and prognostic testing. • Ranolazine is not a first-line drug and should be used in conjunction with a cardiologist.
American College of Cardiology /American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina[4] (2007)**	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established CAD should be treated with blood pressure medication(s) as tolerated, including ACE inhibitors and/or β-blockers with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • ARBs are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a MI and have a LVEF of ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a MI, acute coronary syndrome or left

Clinical Guideline	Recommendations
	ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease. • No recommendation was made regarding the use of ranolazine.
American College of Cardiology/American Heart Association: **2002 Guideline Update for the Management of Patients With Chronic Stable Angina[5] (2002)**	• Aspirin 75 to 325 mg should be used routinely in all patients with acute and chronic ischemic heart disease unless contraindicated. Clopidogrel may be used when aspirin is contraindicated. • β-blockers should be considered as initial therapy for chronic stable angina. • HMG-CoA reductase inhibitors should be recommended even in mild-to-moderate elevations of low-density lipoprotein cholesterol. • ACE inhibitors should be prescribed to patients with diabetes and/or left ventricular systolic dysfunction. • There is insufficient evidence for using an angiotensin receptor blocker in chronic stable angina. • Use sublingual nitroglycerin (NTG) or NTG spray for immediate relief of angina. • Long-acting calcium channel blockers or long-acting nitrates may be used if β-blockers are contraindicated. • An immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • A long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • The use of ranolazine for the treatment of angina was not addressed. This guideline was published before ranolazine was approved for use in the United States.
American College of Physicians: **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease[6] (2004)**	• β-blockers should be strongly considered as initial therapy, unless contraindicated. • ACE inhibitors should be recommended for patients with symptomatic chronic stable angina to prevent MI and death and to reduce symptoms of angina, and in patients with asymptomatic chronic stable angina with coronary artery disease, who also have diabetes mellitus, systolic dysfunction, or both. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful or if β-blockers are contraindicated. • Sublingual NTG or NTG spray for immediate symptomatic relief of angina. • The use of ranolazine was not addressed in this guideline as it was published before ranolazine was approved for use in the United States.
European Society of Cardiology: **Management of Stable Angina Pectoris[7] (2006)**	<u>Therapy to improve prognosis</u> • Aspirin 75 mg once daily is recommended in all patients without contraindications. • Statin therapy is recommended for all patients with coronary disease. • ACE inhibitor therapy is recommended for patients with indications for ACE inhibition including hypertension, heart failure, left ventricular dysfunction and history of myocardial infarction with left ventricular dysfunction and diabetes. • β-blocker therapy is recommended in patients with history of myocardial infarction or heart failure. • Class IIa evidence includes ACE inhibition in patients with angina and proven coronary disease, clopidogrel in patients with stable angina who are not candidates for aspirin and high dose statin therapy in high

Clinical Guideline	Recommendations
	risk patients with proven coronary disease. • Class IIb evidence includes fibrates in patients with low high density lipoprotein cholesterol and high triglycerides who have diabetes or metabolic syndrome. • Calcium channel blockers may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction and who do not have heart failure. <u>Therapy to improve symptoms and/or reduce ischemia</u> • Short-acting NTG therapy is recommended for acute symptom relief and situational prophylaxis. • Test the effects of a β1 blocker and titrate to full dose; consider the need for 24-hour protection against ischemia. • If β-blockers are not effective or not tolerated, attempt monotherapy with a calcium channel blocker, long-acting nitrate or nicorandil*. • If the effects of β-blocker therapy are insufficient, add a dihydropyridine calcium channel blocker. • Class IIa evidence includes a sinus node inhibitor in the case of β-blocker intolerance, or a long-acting nitrate or nicorandil* in place of a calcium channel blocker in the case of insufficient response to calcium channel blocker monotherapy or combination therapy with a calcium channel blocker and β-blocker. • Class IIb evidence includes the use of metabolic agents where available as add-on therapy or in place of conventional therapy when conventional therapy is not tolerated. <u>Treatment of syndrome X</u> • Therapy with nitrates, β-blockers and calcium channel blockers alone or in combination is recommended. • Statin therapy is recommended in patients with hyperlipidemia. • ACE inhibitors are recommended in patients with hypertension. • Class IIa evidence includes a trial of other anti-anginal agents such as nicorandil and metabolic agents. <u>Treatment of vasospastic angina</u> • Treatment with calcium channel blockers is recommended in patients whose coronary arteriogram is normal or shows only non-obstructive lesions. • The use of ranolazine for the treatment of angina was not addressed.
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **2007 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-segment Elevation Myocardial Infarction[8] (2007)**	<u>Immediate management</u> • Low-risk patients that are referred to outpatient stress testing should be given medications such as sublingual nitroglycerin, aspirin and/or β-blockers as a preventative measure. <u>Early hospital care-recommendations for anti-ischemic therapy</u> • Patients with unstable angina/non-ST-segment myocardial infarction (NSTEMI) with ongoing ischemic discomfort should receive sublingual NTG every five minutes for a total of three doses, after which assessment should be about the need for intravenous NTG. Intravenous NTG is indicated in the first 48 hours after unstable angina/NSTEMI for treatment of persistent ischemic, heart failure, or hypertension. • Oral β-blocker therapy should be initiated within the first 24 hours for patients who do not have one or more of the following: 1) signs of

Clinical Guideline	Recommendations
	heart failure, 2) evidence of a low-output state, 3) increased risk for cardiogenic shock, or 4) other relative contraindications to β blockade. • In unstable angina/NSTEMI patients with continuing or frequently recurring ischemia and in whom β-blockers are contraindicated, a nondihydropyridine calcium channel blocker should be given as initial therapy in the absence of clinically significant left ventricular dysfunction or other contraindications. • Oral long-acting nondihydropyridine calcium channel blockers are reasonable for use in unstable angina/NSTEMI patients for recurrent ischemic in the absence of contraindications after β-blockers and nitrates have been fully used. • Use of extended-release forms of nondihydropyridine calcium channel blockers instead of a β-blocker may be considered in patients with unstable angina/NSTEMI. Immediate-release dihydropyridine calcium channel blockers in the presence of adequate β-blockade may be considered in patients with unstable angina/NSTEMI with ongoing ischemic symptoms or hypertension. • An ACE inhibitor should be administered orally within the first 24 hours to unstable angina/NSTEMI patients with pulmonary congestion or LVEF ≤40%, in the absence of hypotension or known contraindications. An ARB should be administered in patients who are intolerant to ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF ≤40%. • An oral ACE inhibitor administered within the first 24 hours of unstable angina/NSTEMI can be useful in patients without pulmonary congestion or LVEF ≤40% in the absence of hypotension or known contraindications. • Ranolazine may be safely administered for symptom relief after unstable angina/NSTEMI, but it does not appear to significantly improve the underlying disease substrate. <u>Late hospital care, hospital discharge, and post-hospital discharge care</u> • All post-unstable angina/NSTEMI patients should be given sublingual or spray NTG and instructed in its use. • β-blockers are indicated for all patients recovering from unstable angina/NSTEMI unless contraindicated. Therapy should be continued indefinitely. • ACE inhibitors should be given and continued indefinitely for patients recovering unstable angina/NSTEMI with heart failure, left ventricular dysfunction, hypertension, or diabetes, unless contraindicated. An ARB should be prescribed at discharge in patients who are intolerant to ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF ≤40%. • NTG to treat ischemic symptoms is recommended. • Calcium channel blockers are recommended for ischemic symptoms when β-blockers are not successful. • Calcium channel blockers are recommended for ischemic symptoms when β-blockers are contraindicated or cause unacceptable side effects. • The use of ranolazine was not addressed in late hospital care, hospital discharge, and post-hospital discharge care. Note: A focused update to the 2007 guideline was published in 2012; however, the recommendations above were not updated and remain current to the 2007 guideline. The 2012 focused update focuses on antiplatelet and anticoagulant therapies.[9]

Clinical Guideline	Recommendations
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-segment Elevation[10] (2011)**	Anti-ischemic drugs • Oral or intravenous nitrate treatment is indicated to relieve angina. Intravenous nitrates are recommended in patients with recurrent angina and/or signs of heart failure. • Patients on chronic β-blocker therapy admitted with acute coronary syndrome should be continued on β-blocker therapy if not in Killip class ≥III. • Oral β-blocker therapy is indicated in all patients with left ventricular dysfunction, unless contraindications are present. • Calcium channel blockers are recommended for relief of symptoms in patients already receiving nitrates and β-blocker therapy, and in patients with contraindications to β-blockade. • Calcium channel blockers are recommended in patients with vasospastic angina. • Intravenous β-blocker therapy at the time of admission should be considered for patients with stable hemodynamics with hypertension and/or tachycardia. • Nifedipine, or other dihydropyridines, are not recommended unless combined with β-blockers. • The role of ranolazine was not included in specific recommendations within the guideline. It was noted that ranolazine exerts antianginal effects by inhibiting the late sodium current. Ranolazine was not effective in reducing major cardiovascular events in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-TIMI 36 trial, but it did reduce the rate of recurrent ischemia.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous cardiac drugs are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Cardiac Drugs, Miscellaneous[2]

Indication	Ranolazine
Treatment of chronic angina	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous cardiac drugs are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cardiac Drugs, Miscellaneous[11]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ranolazine	55	62	Intestines (rapid and extensive, % not reported) Liver (rapid and extensive, % not reported)	Renal (75) Feces (25)	7.0 to 8.9

V. Drug Interactions

Significant drug interactions with the miscellaneous cardiac drugs are listed in Table 5.

Table 5. Significant Drug Interactions with the Cardiac Drugs, Miscellaneous[12]

Generic Name(s)	Significance Level	Interaction	Mechanism
Ranolazine	1	Azole antifungals	Certain azole antifungals inhibit the metabolism of ranolazine, increasing plasma concentrations of ranolazine and the risk of toxicity.
Ranolazine	1	HMG-CoA reductase inhibitors	Ranolazine inhibits the metabolism of certain HMG-CoA reductase inhibitors, increasing plasma concentrations of HMG-CoA reductase inhibitors and the risk of adverse reactions.
Ranolazine	1	Macrolides and related antibiotics	Macrolide antibiotics inhibit the metabolism of ranolazine by the cytochrome P450 (CYP) 3A system. Concomitant use may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	1	Nefazodone	Plasma concentrations and pharmacologic effects of ranolazine may be increased by coadministration of nefazodone. Inhibition of cytochrome P4503A4 by nefazodone may decrease the metabolic elimination of ranolazine.
Ranolazine	1	Protease inhibitors	Protease inhibitors inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	2	Aprepitant	Plasma concentrations and pharmacologic effects of ranolazine may be increased by coadministration of aprepitant. Inhibition of CYP3A4 by aprepitant may decrease the metabolic elimination of ranolazine.
Ranolazine	2	Barbiturates	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by barbiturates. Induction of CYP3A isoenzymes by barbiturates may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Carbamazepine	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by carbamazepine. Induction of CYP3A isoenzymes by carbamazepine may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Diltiazem	Diltiazem inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.
Ranolazine	2	Erythromycin	Pharmacologic effects and plasma

Generic Name(s)	Significance Level	Interaction	Mechanism
			concentrations of ranolazine may be decreased by erythromycin. Induction of cytochrome P450 3A isoenzymes by erythromycin may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Fluconazole	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by fluconazole. Induction of CYP3A isoenzymes by fluconazole may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Hydantoins	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by hydantoins. Induction of CYP3A isoenzymes by hydantoins may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Rifamycins	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by rifamycins. Induction of CYP3A isoenzymes by rifamycins may increase the metabolic elimination of the ranolazine.
Ranolazine	2	Verapamil	Verapamil inhibits the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous cardiac drugs are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Cardiac Drugs, Miscellaneous[2]

Adverse Events	Ranolazine
Cardiovascular	
Bradycardia	0.5 to 4.0
Hypertension	0.5 to 4.0
Orthostatic hypotension	0.5 to 4.0
Palpitation	0.5 to 4.0
Syncope	0.5 to 4.0
Central Nervous System	
Confusional state	0.5 to 4.0
Dizziness	✔
Headache	5.5
Vertigo	0.5 to 4.0
Gastrointestinal	
Abdominal pain	0.5 to 4.0
Anorexia	0.5 to 4.0
Constipation	4.5
Dry mouth	0.5 to 4.0
Dyspepsia	0.5 to 4.0

Adverse Events	Ranolazine
Nausea	4.4
Vomiting	0.5 to 4.0
Respiratory	
Dyspnea	0.5 to 4.0
Other	
Asthenia	0.5 to 4.0
Blurred vision	0.5 to 4.0
Hematuria	0.5 to 4.0
Hyperhidrosis	0.5 to 4.0
Peripheral edema	0.5 to 4.0
Tinnitus	0.5 to 4.0

✔ Percent not specified.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous cardiac drugs are listed in Table 7.

Table 7. Usual Dosing Regimens for the Cardiac Drugs, Miscellaneous[2]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ranolazine	<u>Treatment of chronic angina:</u> Extended-release tablet, initial, 500 mg twice daily; maximum: 1,000 mg twice daily	Safety and efficacy in children have not been established.	Extended-release tablet: 500 mg 1,000 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous cardiac drugs are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Cardiac Drugs, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chaitman et al.[13] (2004) CARISA Ranolazine ER 750 to 1,000 mg BID in combination with diltiazem, atenolol, or amlodipine vs placebo in combination with diltiazem, atenolol, or amlodipine	DB, MC, PC, PG, RCT Patients with symptomatic chronic angina despite treatment with diltiazem, atenolol, or amlodipine	N=823 12 weeks with long-term follow-up of up to 39 months	Primary: Exercise duration on treadmill Secondary: Time to inset of angina, time to ≥1 mm ST-segment depression, angina frequency, nitroglycerin use, survival	Primary: In the ranolazine group, exercise duration was significantly increased compared to placebo (P=0.01). Secondary: Time to angina and time to 1 mm ST-segment depression were significantly increased compared to placebo. Treatment with ranolazine significantly reduced the frequency of angina attacks (3.3 vs 2.5 attacks per week for the 750 mg group; P=0.006; and 3.3 vs 2.1 attacks per week for the 1,000 mg group; P<0.001), and nitroglycerin use compared to placebo. The most common adverse effects were constipation, dizziness, nausea, and asthenia (≤7.3% in the ranolazine group vs ≥0.7% in the placebo group). The survival rates for patients taking ranolazine were 98.4% (95% CI, 97.4 to 99.5) at year one and 95.9% (95% CI, 94.0 to 97.7) at year two.
Timmis et al.[14] (2006) CARISA Ranolazine ER 750 to 1,000 mg BID in combination with diltiazem, atenolol, or amlodipine vs placebo in	Post-hoc analysis of CARISA Patients with type 2 diabetes who had symptomatic chronic angina despite treatment with diltiazem, atenolol, or amlodipine	N=823 12 weeks with long-term follow-up of up to 39 months	Primary: Exercise duration on treadmill Secondary: Time to onset of angina, time to ≥1 mm ST-segment depression, angina frequency, nitroglycerin usage, and HbA_{1c} levels in diabetic	Primary: In the CARISA trial, 23% of the patients were diabetic and 77% were not diabetic. The effects of ranolazine in the diabetic patients were comparable to those in the nondiabetic patients. There was no significant difference between the diabetic and nondiabetic patients in exercise duration (P=0.89), time to onset of angina (P=0.54), or time to ≥1 mm ST-segment depression (P=0.44). There was also no difference in the diabetic patients compared to the nondiabetic patients in angina frequency (P=0.81) or nitroglycerin consumption (P=0.063). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
combination with diltiazem, atenolol, or amlodipine			patients only and lipid panel as post hoc analysis	Compared to placebo, there were significant reductions in the HbA_{1c} levels in the ranolazine 750 mg (P=0.008) and ranolazine 1,000 mg (P=0.0002) treatment groups. A subgroup analysis showed that there were significant reductions in the HbA_{1c} levels in insulin-dependent diabetics treated with ranolazine (P=0.016 in the 750 mg group and P=0.008 in the 1,000 mg group). The non-insulin-dependent patients in the ranolazine-treated group showed a significant reduction in HbA_{1c} with the 1,000 mg dose (P=0.007), but not with the 750 mg dose (P=0.087). Treatment with ranolazine 750 mg was associated with an increase in low-density lipoprotein and total cholesterol, while treatment with ranolazine 1,000 mg did not have any effects on the lipids profile.
Stone et al.[15] (2006) ERICA Ranolazine ER 1,000 mg BID in combination with amlodipine vs placebo in combination with amlodipine	DB, PC, PG, RCT Stable patients with coronary disease and ≥3 anginal attacks per week despite maximum recommended dosage of amlodipine	N=565 6 weeks	Primary: Frequency of angina episodes per week Secondary: Average weekly nitroglycerin consumption rate, SAQ, safety as assessed by adverse events and electrocardiogram	Primary: Angina frequency at baseline averaged 5.63 episodes per week. Treatment with ranolazine significantly reduced the frequency of angina episodes per week compared to placebo (2.88 vs 3.31; P=0.028). Secondary: Nitroglycerin consumption use at baseline averaged 4.72 tablets per week. Ranolazine treatment significantly reduced the use of nitroglycerin compared to placebo (2.03 vs 2.68; P=0.014). The SAQ scores on angina frequency were significantly improved in the ranolazine arm compared to placebo arm (P=0.008). There were no significant differences between treatment groups in the other SAQ measures, such as physical limitation, anginal stability, disease perception, and treatment satisfaction.
Chaitman et al.[16] (2004) MARISA Ranolazine ER 500 to 1,500 mg BID vs	DB, PC, RCT, XO Patients with coronary artery disease and ≥3 month history of effort angina that had previously responded to antianginal agents	N=191 4 weeks with long-term follow-up of up to 36 months	Primary: Exercise duration Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak, exercise duration at	Primary: Treatment with ranolazine at all doses resulted in significant increases in exercise duration (P<0.001). Secondary: Treatment with ranolazine at all doses resulted in significant increases in time to angina (P<0.001) and time to 1 mm ST-segment depression (P<0.001). No clinically significant changes in heart rate or BP at rest or exercise

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo Patients discontinued anti-anginal medications prior to randomization.			peak, long-term survival	were observed. The rates of adverse events were similar for the 500 mg and placebo group, but higher with the 1,000 and 1,500 mg groups (15.6% for placebo, 16.0% for 500 mg, 21.7% for 1,000 mg, and 34.2% for 1,500 mg). The survival rates were 96.3% (95% CI, 93.0 to 99.5) at one year and 93.6% (95% CI, 89.3 to 98.0) at two years.
Koren et al.[17] (2007) Ranolazine ER 500 to 1,000 mg BID	MC, OL Patients with chronic angina who had completed the MARISA or CARISA trial	N=746 2.82 years (mean duration)	Primary: Discontinuation, adverse events, electrocardiogram findings, and mortality	Primary: 571 patients (76.7%) remained on therapy while 72 patients (9.7%) discontinued due to adverse events two years after initial dosing. There was a significant correlation between patient age >64 years and increased rates of discontinuation related to adverse events (RR, 2.32; P<0.001). A significantly lower correlation of adverse event-related discontinuation was seen in patients with a history of congestive heart failure (RR, 0.55; P=0.030). Compared to baseline, a mean prolongation of approximately 2.4 microseconds in the QT interval was observed (P<0.001). However there were no significant differences in PR or QRS intervals during this time. A total of 64 deaths (all causes) occurred during the 2,102 patient-years (3.0% annual incidence) of the study. This translates to a 97.2% and 94.4%, one- and two-year survival from this incidence.
Rich et al.[18] (2007) Ranolazine ER 750 to 1,000 mg BID vs placebo	MA Patients ≥70 years of age with symptomatic chronic angina despite treatment diltiazem, atenolol, or amlodipine	N=1,387 (2 trials) 6 weeks	Primary: Improvement in younger patients (<70 years of age) and older patients (≥70 years of age) in exercise times, angina frequency, and adverse events Secondary: Not reported	Primary: Overall ranolazine significantly improved exercise duration and time to onset of angina during exercise testing (P≤0.03). There was no difference on exercise time in younger patients compared to older patients (P>0.8). Older patients tended to have fewer angina episodes (a mean of 3.21 in the placebo group and 2.08 in the ranolazine 1,000 mg group) than younger patients (a mean of 4.16 in the placebo group and 3.11 in the ranolazine 1,000 mg group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were more commonly reported in the older patient population (32.6% in the placebo group and 44.2% in the ranolazine group) compared to the younger patients (31.2% in the placebo group and 32.1% in the ranolazine group). Secondary: Not reported
Cocco et al.[19] (1992) Ranolazine IR* 10, 60, 120, or 240 mg single dose in addition to beta-blocker or diltiazem vs placebo in addition to beta-blocker or diltiazem	DB, MC, PC, RCT, XO Patients with chronic stable angina who remained symptomatic despite treatment with beta-blockers or diltiazem	N=104 4 to 9 days	Primary: Exercise duration, time to angina, time to ≥1 mm ST-segment depression Secondary: Heart rate, BP	Primary: Exercise duration, time to angina, and time to 1 mm ST-segment depression were significantly improved with ranolazine 240 mg dose only in the beta-blocker group and the groups combined (P<0.05 for both). There was no significant difference in exercise duration, time to angina, or time to 1 mm ST-segment depression with ranolazine treatment in patients that were on the diltiazem regimen (P>0.05 for all). Secondary: Treatment with ranolazine did not result in significant changes in heart rate or BP compared to placebo (P>0.05).
Pepine et al.[20] (1999) Ranolazine IR* 400 mg BID, 267 mg TID, or 400 mg TID vs placebo	DB, MC, PC, RCT, XO Patients with chronic stable angina that responded to conventional antianginal therapy	N=312 5 weeks	Primary: Time to angina onset, exercise duration, and time to 1 mm ST-segment depression at peak and trough concentrations Secondary: Safety	Primary: At peak ranolazine concentrations, time to angina onset (P≤0.02), exercise duration (P=0.013), and time to 1 mm ST-segment depression were significantly improved with all dosing regimens. At trough ranolazine concentrations, only time to 1 mm ST-segment depression was significantly improved (P=0.047). Secondary: The rates of adverse effects were similar in the ranolazine groups and placebo group. Only minor gastrointestinal adverse effects were reported more frequently with ranolazine than placebo (6.6to 10.7 vs 3.2%).
Rousseau et al.[21] (2005)	DB, MC, PC, XO Patients with	N=158 7 to 10 days	Primary: Time to onset of angina	Primary: Treatment with ranolazine and atenolol both resulted in significant increases in time to angina, exercise duration, and time to 1 mm ST-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ranolazine IR* 400 mg TID for 7 to 10 days vs atenolol 100 mg QD for 7 to 10 days vs placebo for 7 to 10 days	coronary artery disease and chronic angina who were on standard doses of atenolol		Secondary: Time to 1 mm ST-segment depression, total exercise duration, angina frequency, nitroglycerin use	segment depression when compared to placebo (P<0.05 for all). Secondary: There was no significant difference between ranolazine and atenolol in the time to angina (P=0.18), time to 1 mm ST-segment depression (P=0.86), angina frequency, or nitroglycerin use. However, the increase in exercise duration was significantly greater in the ranolazine group than atenolol (mean difference of 21.1 seconds, 95% CI, 6.2 to 36.0; P=0.006).
Morrow et al.[22] (2007) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine ER 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	DB, MC, PC, RCT Patients ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-STEMI ≥3)	N=6,560 1 year	Primary: Composite of cardiovascular death, MI, or recurrent ischemia Secondary: Composite of cardiovascular death, MI, or severe recurrent ischemia, rate of failure of therapy (cardiovascular death, MI, recurrent ischemia, positive Holter for ischemia, hospitalization for new or worsening heart failure, or an early positive ETT),	Primary: The composite of cardiovascular death, MI or recurrent ischemia occurred in 21.8% of the patients in the ranolazine group and 23.5% of patients in the placebo group (HR, 0.92; 95% CI, 0.83 to 1.02; P=0.11). Secondary: The composite of cardiovascular death, MI, or severe recurrent ischemia occurred in 18.7% of patients in the ranolazine group compared to 19.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.86 to 1.08; P=0.50). Failure of therapy occurred in 36.8% of patients in the ranolazine group and 38.3% of patients in the placebo group (HR, 0.94; 95% CI, 0.87 to 1.02; P=0.16). Cardiovascular death occurred in 4.4% of patients in the ranolazine group and 4.5% of patients in the placebo group (HR, 1.00; 95% CI, 0.79 to 1.25; P=0.98). MI occurred in 7.4% of patients in the ranolazine group and 7.6% of patients in the placebo group (HR, 0.97; 95% CI, 0.81 to 1.16; P=0.76). Recurrent ischemia occurred in 13.9% of patients in the ranolazine group and 16.1% of patients in the placebo group (HR, 0.97; 95% CI, 0.76 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			safety	0.99; P=0.03). There was no difference in the documented symptomatic arrhythmias in the ranolazine group (3.0%) and the placebo group (3.1%; P=0.84).
Scirica et al.[23] (2007) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine ER 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	DB, MC, PC, RCT Patients ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-STEMI ≥3)	N=6,560 7 days	Primary: Incidence of clinically significant arrhythmias Secondary: Not reported	Primary: Ventricular tachycardia ≥3 beats ≥100 bpm was significantly less in the ranolazine group (52.1%) compared to placebo (60.6%) (RR, 0.86; 95% CI, 0.82 to 0.90; P<0.001). Ventricular tachycardia ≥4 beats ≥100 bpm was significantly less in the ranolazine group (20.9%) compared to placebo (29.5%) (RR, 0.71; 95% CI, 0.6 to 0.78; P<0.001). Ventricular tachycardia ≥8 beats (lasting <30 seconds) was significantly less in the ranolazine group (5.3%) compared to placebo (8.3%) (RR, 0.63; 95% CI, 0.52 to 0.76; P<0.001). There was no significant difference in polymorphic ventricular tachycardia ≥8 beats in the ranolazine group (1.2%) compared to placebo (1.4%) (RR, 0.83; 95% CI, 0.54 to 1.28; P=0.40). There was no significant difference in sustained ventricular tachycardia (≥30 seconds) in the ranolazine group (0.44%) compared to placebo (0.44%) (RR, 1.01; 95% CI, 0.48 to 2.13; P=0.98). This includes monomorphic (0.13 vs 0.22%; RR, 0.59; 95% CI, 0.17 to 2.06; P=0.37) and polymorphic (0.32 vs 0.22%; RR, 1.41; 95% CI, 0.52 to 3.78; P=0.46). There was no significant difference in new-onset AF in the ranolazine group (1.7%) compared to placebo (2.4%) (RR, 0.74; 95% CI, 0.52 to 1.05; P=0.08). Other supraventricular arrhythmias ≥120 bpm lasting at least 4 beats were significantly less in the ranolazine group (44.7%) compared to placebo (55.0%) (RR, 0.81; 95% CI, 0.77 to 0.85; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Wilson et al.[24] (2009) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine ER 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	Subgroup analysis of MERLIN-TIMI 36 of patients with a history of prior chronic angina Patients ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-STEMI ≥3)	N=3,565 1 year	Primary: Time to first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia Secondary: Anginal episodes, need for an increase or addition of any antianginal therapy, and exercise duration on treadmill or bicycle ETT performed at 8 months, safety, incidence of clinically significant arrhythmias	Primary: The time to the first occurrence of the composite of cardiovascular death, MI, or recurrent ischemia was lower in patients treated with ranolazine compared to placebo among patients with prior angina (25.2 vs 29.4%, respectively, HR, 0.86; 95% CI, 0.75 to 0.97; P=0.017). This effect was due to the effects of ranolazine on recurrent ischemia. Ranolazine had no effect on the risk of cardiovascular death or MI among patients with prior angina (HR, 0.97; 95% CI, 0.80 to 1.16; P=0.71). Secondary: Ranolazine reduced the incidence of recurrent ischemia (HR, 0.78; 95% CI, 0.67 to 0.91; P=0.002), worsening angina (HR, 0.77; 95% CI, 0.59 to 1.00; P=0.048), and intensification of antianginal therapy (HR, 0.77; 95% CI, 0.64 to 0.92, P=0.005) compared to placebo among patients with prior angina. Ranolazine improved severe recurrent ischemia compared to placebo among patients with prior angina (11.9 vs 14.4%, respectively; HR, 0.81; 95% CI, 0.67 to 0.98; P=0.026). The mean number of traditional antianginal agents was decreased with ranolazine compared to placebo among patients with prior angina (2.8 vs 2.9, respectively; P=0.045). Ranolazine significantly improved all metrics of exercise performance on ETT or bicycle exercise testing compared to placebo among patients with prior angina. Ranolazine was generally well tolerated in patients with prior angina. The most common adverse effects with ranolazine compared to placebo were dizziness (12.4 vs 7.4%, respectively), nausea (9.7 vs 6.1%, respectively), and constipation (8.5 vs 3.3%, respectively). No significant increase in frequency of symptomatic documented arrhythmias was observed with ranolazine compared to placebo among patients with prior angina (risk ratio, 0.98; 95% CI, 0.67 to 1.43; P=0.92).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Clinically significant arrhythmias were significantly lower in the ranolazine group (73.9 vs 83.1%, respectively; P=0.0001).
Mega et al.[25] (2010) MERLIN-TIMI 36 Ranolazine IV* administered for 12 to 96 hours, followed by ranolazine ER 1,000 mg orally BID vs placebo Study medication was administered in addition to standard therapy.	Subgroup analysis of MERLIN-TIMI 36 of women Women ≥18 years of age with myocardial ischemia at rest (≥10 minutes) who had ≥1 indicator of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-STEMI ≥3)	N=2,291 1 year	Primary: Time to first occurrence of any element of the composite of cardiovascular death, MI, or recurrent ischemia in women Secondary: Anginal episodes, incidence of clinically significant arrhythmias	Primary: Treatment with ranolazine was associated with a 29% reduction in recurrent ischemia in women compared to placebo (13.0 vs 18.2%; HR, 0.71; 95% CI, 0.57 to 0.88; P=0.002). There was no significant reduction in cardiovascular death or MI with ranolazine compared to placebo in women (P=0.80). Secondary: Treatment with ranolazine was associated with less angina compared to placebo in women (P<0.001). Fewer women treated with ranolazine needed to undergo intensification of their antianginal medical regimen compared to placebo (10.4 vs 14.4%, respectively; P=0.003). There was no difference in symptomatic documented arrhythmias in women treated with ranolazine vs placebo (2.6 vs 2.6%, respectively; P=0.95). Treatment with ranolazine was associated with fewer episodes of ventricular arrhythmias compared to placebo (P=0.008).
Metha et al.[26] (2011) Ranolazine for 4 weeks vs placebo for 4 weeks	DB, PC, XO (pilot trial) Women with angina, evidence of myocardial ischemia (signs and symptoms), but no obstructive coronary artery disease	N=20 10 weeks	Primary: Seattle Angina Questionnaire, cardiac magnetic resonance Secondary: Not reported	Primary: Patients receiving ranolazine had significantly higher (better) Seattle Angina Questionnaire scores, including physical functioning (P=0.046), angina stability (P=0.008), and QOL (P=0.021). There was a trend toward a higher (better) cardiac magnetic resonance mid-ventricular myocardial perfusion reserve index (2.4 vs 2.1; P=0.074) with ranolazine. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended release, IR=immediate-release, IV=intravenous, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SR=sustained-release, XO=cross-over
Miscellaneous abbreviations: AF=atrial fibrillation, BP=blood pressure, CI=confidence interval, ETT=exercise tolerance test, HbA_{1c}=glycosylated hemoglobin, HR=hazard ratio, MI=myocardial infarction, QOL=quality of life, RR=relative risk, SAQ=Seattle Angina Questionnaire, STEMI=ST-elevation myocardial infarction, TIMI=thrombolysis in myocardial infarction

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Cardiac Drugs, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ranolazine	extended-release tablet	Ranexa®	$$$$$	N/A

N/A=Not available.

X. Conclusions

Ranolazine is the only miscellaneous cardiac drug currently available and it is approved for the treatment of chronic angina. It may be used in combination with β-blockers, nitrates, calcium channel blockers, antiplatelet therapy, lipid lowering therapy, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers. The exact mechanism of ranolazine is unknown. The anti-ischemic and antianginal effects do not depend upon reductions in heart rate or blood pressure.[2] Ranolazine is not available in a generic formulation.

There are several organizations that provide recommendations on the treatment of chronic angina. β-blockers are considered first-line therapy for reducing symptoms of angina in patients with coronary artery disease. Long-acting calcium channel blockers or long-acting nitrates may be used in combination with β-blockers if initial therapy is not successful, or if β-blockers are contraindicated. The available guidelines do not provide specific recommendations regarding the use of ranolazine for the treatment of chronic angina, as it was either approved by the Food and Drug Administration after their publication dates or it has not been approved in their host countries.[3-6] The American College of Cardiology/American Heart Association guideline on unstable angina and non-ST-segment myocardial infarction (NSTEMI) states that ranolazine may be safely administered for symptom relief after unstable angina/NSTEMI, but it does not appear to significantly improve the underlying disease.[8]

Three trials have evaluated the efficacy and safety of ranolazine SR in patients with chronic angina. Ranolazine (administered either as monotherapy or in combination with other anti-anginal drugs) was more effective compared to placebo with regards to exercise duration, time to onset of angina, frequency of angina, and nitroglycerin use.[13,15,16] In the MERLIN-TIMI 36 trial, there was no beneficial effect on cardiovascular outcomes with ranolazine compared to placebo in patients with acute coronary syndrome.[2,22] Ventricular arrhythmias were less common with ranolazine; however, this did not lead to a reduction in mortality, arrhythmia hospitalization or arrhythmia symptoms.[2,22,23] Tolerance to ranolazine did not develop after 12 weeks of therapy. Rebound increases in angina, as measured by exercise duration, have not been observed following abrupt discontinuation of ranolazine.[2]

There is insufficient evidence to support that ranolazine is safer or more efficacious than other agents commonly used for the treatment of chronic angina. Since ranolazine is not recommended as first-line therapy for the treatment of chronic angina, it should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous cardiac drugs within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous cardiac drug is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Bile Acid Sequestrants
AHFS Class 240604
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I. Overview

Dyslipidemia is a complex of related conditions that affects many individuals. Low-density lipoprotein cholesterol (LDL-C) is considered the primary target of cholesterol lowering therapy. Many studies have demonstrated that elevated concentrations of LDL-C are a major risk factor for coronary heart disease, and lowering LDL-C will reduce the risk for major coronary events. Non-high-density lipoprotein cholesterol is a secondary target of therapy in patients with elevated triglycerides (≥200 mg/dL). This parameter takes into account the atherogenic potential associated with remnant lipoproteins in patients with hypertriglyceridemia. High-density lipoprotein cholesterol (HDL-C) has been shown to be an independent predictor of cardiovascular mortality and is considered an LDL modifying risk factor; however, there is insufficient data to warrant setting a specific goal for raising HDL-C. The independent effect of raising HDL-C or lowering triglycerides on the risk of cardiovascular morbidity and mortality has not been determined.[1]

The antilipemic agents are categorized into five different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins) and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration-approved indications, mechanism of action, efficacy, safety profiles, tolerability and ease of use.

Bile acids are secreted into the intestines during digestion to emulsify fat and lipids to facilitate their absorption. Most of the bile acids are reabsorbed and returned to the liver via enterohepatic circulation. The bile acid sequestrants bind to bile acids and form a complex, which is then excreted in the feces. The reduction in bile acids increases the oxidation of cholesterol to bile acids.[2-4] There is a subsequent increase in the number of LDL receptors in the liver, which increases hepatic uptake of LDL-C and reduces serum cholesterol levels. Bile acid sequestrants can decrease LDL-C by 15 to 30% and increase HDL-C by 3 to 5%. Triglycerides may increase or remain unchanged.[1]

The bile acid sequestrants that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Cholestyramine (regular and light) and colestipol are available in a generic formulation. This class was last reviewed in August 2010.

Table 1. Bile Acid Sequestrants Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cholestyramine	packet for oral suspension, powder for oral suspension	Questran®*†, Questran Light®*‡	cholestyramine, cholestyramine light
Colesevelam	packet for oral suspension, tablet	Welchol®	none
Colestipol	granules for oral suspension, packet for oral suspension, tablet	Colestid®*	colestipol

*Generic is available in at least one dosage form or strength.
†Contains sucrose.
‡Contains aspartame.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the bile acid sequestrants are summarized in Table 2.

Table 2. Treatment Guidelines Using the Bile Acid Sequestrants

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[5] (2004)**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia.

Clinical Guideline	Recommendation
	Treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report[1] (2002)**	General recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association’s recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL).

Clinical Guideline	Recommendation
	• Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <u>Omega-3 fatty acids</u> • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update[6] (2011)**	<u>Lipid management</u> • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be

Clinical Guideline	Recommendation
	reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults[7] (2011)**	Clinical highlights • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures. • Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established coronary artery disease, non-cardiac atherosclerosis, or coronary artery disease equivalent. Ongoing drug therapy • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30% reduction in CHD events. Monotherapy • Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy. • Specific statin and dose should be selected based on cost and amount of lipid-lowering required. • If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. • Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. • Long-term use of niacin is usually limited for many patients due to side

Clinical Guideline	Recommendation

	effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc).
	• Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin.
	• Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate).
	• Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease.
	• The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin.
	• The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown.
	• Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most potent with a statin.
	• Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after.
	
	<u>Combination therapy</u>
	• It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe.
	    ○ A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy.
	    ○ No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events.
	    ○ The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints.
	• Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy.
	• Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit.
	• There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins.
	• No randomized-controlled trials looking at clinical vascular endpoints

Clinical Guideline	Recommendation
	are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy. Lifestyle modifications • Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss. • Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range. • A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended. • Vitamin E supplementation should not be used. • Light to moderate consumption of alcohol may lower CHD rates. • Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association[8] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice[9] (2012)**	Drugs • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. • Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. • Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. Drug combinations

Clinical Guideline	Recommendation
	• Patients with dyslipidemia, particularly those with established cardiovascular disease, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
National Institute for Health and Clinical Excellence: **Lipid Modification[10] (2010)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of cardiovascular disease for adults who have a ≥20% 10 year risk of developing cardiovascular disease. • Treatment for the primary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of cardiovascular disease. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of cardiovascular disease. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of cardiovascular disease. • Statin therapy is recommended for adults with clinical evidence of cardiovascular disease. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dL) or LDL-C <2 mmol/L (<77 mg/dL) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with cardiovascular disease who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart	<u>Risk factor control for all patients with transient ischemic attack (TIA) or</u>

Clinical Guideline	Recommendation
Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[11] (2011)**	ischemic stroke • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD. • For patients with atherosclerotic ischemic stroke or TIA without known CHD, it is reasonable to target a reduction of ≥50% in LDL-C or a target LDL-C level <70 mg/dL to obtain maximal benefit. • Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to the National Cholesterol Education Program III guidelines (i.e., lifestyle modification, dietary guidelines, medication recommendations). • Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil.
American Association of the Study of Liver Disease: **Primary Biliary Cirrhosis[12] (2009)**	• Ursodeoxycholic acid therapy is the only Food and Drug Administration-approved agent for the treatment of primary biliary cirrhosis. It is currently supported by the most data and is recommended for use in appropriately selected patients who have abnormal liver chemistry. • Issues of patient compliance, development of superimposed liver disease, or coadministration with bile sequestrants (e.g., cholestyramine or colestipol) should be considered for patients with suboptimal response. • Pruritus is a complication of primary biliary cirrhosis and cholestyramine is the drug of choice for the treatment of this complication. Alternative treatments of pruritus include rifampin, opioid antagonists, and liver transplantation.

American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: **An Algorithm for Glycemic Control[13] (2009)**	Management of patients With glycosylated hemoglobin (HbA_{1c}) levels of 6.5 to 7.5%
	• Monotherapy:
	    ○ Metformin is the cornerstone of monotherapy because of its safety and efficacy.
	• Dual therapy:
	    ○ Metformin is the cornerstone of dual therapy.
	    ○ The second component of the dual therapy regimen includes either an incretin mimetic, dipeptidyl peptidase-4 inhibitor, or an insulin secretagogue.
	    ○ Additional dual therapy regimens include (1) metformin combined with colesevelam, and (2) metformin combined with an alpha glucosidase inhibitor. These regimens have a minimal risk of hypoglycemia and colesevelam lowers LDL-C.
	• Insulin therapy:
	    ○ Colesevelam is unlikely to contribute to the effectiveness of insulin.
	
	Management of patients with HbA_{1c} levels of 7.6 to 9.0%
	• Colesevelam is not considered in this HbA_{1c} range due to its limited HbA_{1c} -lowering potential.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the bile acid sequestrants are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Bile Acid Sequestrants[2-4,14]

Indication	Cholestyramine	Colesevelam	Colestipol
Hypercholesterolemia			
Adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia as monotherapy or in combination with an HMG CoA reductase inhibitor (statin)		✔	
Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated LDL-C) who do not respond adequately to diet	✔ *		
Adjunctive therapy to diet for the reduction of elevated serum total cholesterol and LDL-C in patients with primary hypercholesterolemia (elevated LDL-C) who do not respond adequately to diet			✔
Monotherapy or in combination with a statin to reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: 1) LDL-C remains ≥190 mg/dL or LDL-C remains ≥160 mg/dL and 2) there is a positive family history of premature cardiovascular disease or two or more other cardiovascular disease risk factors are present in the pediatric patient		✔	
Miscellaneous			
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus		✔ †	
Relief of pruritus associated with partial biliary obstruction	✔		

*May be useful to lower LDL-C in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.
†Colesevelam has not been studied in type 2 diabetes as monotherapy or in combination with a dipeptidyl peptidase-4 inhibitor and has not been extensively studied in combination with thiazolidinediones.

IV. Pharmacokinetics

The pharmacokinetic parameters of the bile acid sequestrants are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Bile Acid Sequestrants[2-4,14,15]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Cholestyramine	0	Not reported	None	Not reported	Not reported
Colesevelam	0	Not reported	None	Renal (0.05) Feces (majority; % not reported)	Not reported
Colestipol	0	Not reported	None	Renal (<0.05) Feces (100)	Not reported

V. Drug Interactions

Significant drug interactions with the bile acid sequestrants are listed in Table 5.

Table 5. Significant Drug Interactions with the Bile Acid Sequestrants[14]

Generic Name(s)	Significance Level	Interaction	Mechanism
Colesevelam	1	Oral contraceptives	Colesevelam may bind with ethinyl estradiol in the gastrointestinal tract, decreasing ethinyl estradiol absorption, and thus the pharmacologic efficacy of ethinyl estradiol.
Cholestyramine	2	Anticoagulants	Cholestyramine may decrease the gastrointestinal absorption of oral anticoagulants, resulting in lower systemic levels of anticoagulants, and potentially decreasing the effectiveness of the anticoagulant.
Cholestyramine, Colestipol	2	Corticosteroids	Certain bile acid sequestrants may interfere with the gastrointestinal absorption of hydrocortisone, decreasing the therapeutic effect of hydrocortisone.
Cholestyramine	2	Deferasirox	Gastrointestinal absorption and enterohepatic recycling of deferasirox may be decreased due to the formation of physical chemical complexes with cholestyramine. Plasma concentrations and pharmacologic effects of deferasirox may be decreased.
Cholestyramine, Colestipol	2	Digoxin	Cholestyramine and colestipol may decrease gastrointestinal absorption of digoxin, as well as alter the enterohepatic recycling of digoxin. This may result in lower systemic levels of digoxin. In addition, administering colestipol with digoxin may result in a shorter half-life of digoxin, potentially decreasing the effectiveness of digoxin.
Cholestyramine, Colestipol	2	Loop diuretics	Cholestyramine and colestipol may decrease the gastrointestinal absorption of furosemide, due to binding by the anion exchange resins, resulting in lower systemic effects of furosemide. Cholestyramine and furosemide administration should be separated by as much time as possible (at least two hours). Colestipol should be taken as long as possible (at least two hours) after furosemide.
Cholestyramine, Colesevelam	2	Thyroid hormones	Cholestyramine and colesevelam may decrease the gastrointestinal absorption of thyroid hormones by binding to them, resulting in lower systemic levels of thyroid hormones.

Generic Name(s)	Significance Level	Interaction	Mechanism
Cholestyramine	2	Troglitazone	Troglitazone may bind to cholestyramine in the gastrointestinal tract, decreasing troglitazone absorption and thus, the pharmacologic effect of troglitazone.
Cholestyramine	2	Valproic acid	Cholestyramine interferes with the gastrointestinal absorption of valproic acid, decreasing the therapeutic effects of valproic acid.
Colesevelam	2	Cyclosporine	Colesevelam may bind with cyclosporine in the gastrointestinal tract, decreasing the absorption of cyclosporine, and thus the pharmacologic effect of cyclosporine.
Colesevelam	2	Glyburide	Colesevelam may bind with glyburide in the gastrointestinal tract, decreasing the absorption of glyburide, and thus the pharmacologic effect of glyburide.
Colesevelam	2	Hydantoins	Colesevelam may bind to and impair oral absorption of hydantoins and decrease the plasma concentrations of hydantoins.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the bile acid sequestrants are listed in Table 6. Cholestyramine and colestipol can decrease plasma folate levels with long-term administration; therefore, folic acid supplementation may be necessary.[2,4] Bile acid sequestrants may also decrease the absorption of fat-soluble vitamins A, D, E, and K.[2-4]

Table 6. Adverse Drug Events (%) Reported with the Bile Acid Sequestrants[2-4]

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Cardiovascular			
Angina	-	-	✔
Aortic stenosis	-	✔	-
Bradycardia	-	✔	-
Chest pain	-	-	✔
Hypertension	-	2.8	-
Myocardial infarction	-	✔	-
Tachycardia	-	-	✔
Central Nervous System			
Anxiety	✔	-	-
Dizziness	✔	-	✔
Drowsiness	✔	-	-
Fatigue	✔	3.9	✔
Femoral nerve pain	✔	-	-
Headache	✔	3.9 to 7.6	✔
Insomnia	-	-	✔
Light-headedness	-	-	✔
Migraine	-	-	✔
Paresthesia	✔	-	-
Syncope	✔	-	-

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Tinnitus	✔	-	-
Vertigo	✔	-	-
Weakness	-	-	✔
Gastrointestinal			
Abdominal pain/discomfort	✔	-	✔
Abdominal distention	-	-	-
Anorexia	✔	-	✔
Black stools	✔		✔
Bleeding from a known duodenal ulcer	✔	-	-
Bloating	✔	-	✔
Cholecystitis	-	-	✔
Cholelithiasis	✔	-	✔
Constipation	✔	9 to 11	✔
Diarrhea	✔	5	✔
Diverticulitis	✔	-	-
Dyspepsia	-	3.9 to 8.3	-
Dysphagia	✔	-	-
Eructation	✔	-	-
Flatulence	✔		-
Heartburn	-	-	✔
Hemorrhoidal bleeding	✔		✔
Hiccups	✔	-	-
Indigestion	-	-	✔
Intestinal gas	-	-	✔
Intestinal obstruction	✔	-	-
Malabsorption syndrome	✔	-	-
Nausea	✔	3.0 to 4.2	✔
Pancreatitis	✔	-	-
Peptic ulcer	-	-	✔
Rectal bleeding	✔		
Rectal pain	✔	-	-
Sour taste	✔	-	-
Steatorrhea	✔	-	-
Ulcer attack	✔		
Vomiting	✔	2.3	✔
Genitourinary			
Burnt odor to urine	✔	-	-
Diuresis	✔	-	-
Dysuria	✔	-	-
Hematuria	✔	-	-
Hematological			
Anemia	✔	-	-
Ecchymosis	✔		
Hypoprothrombinemia	✔	-	-
Ecchymosis	✔	-	-
Prolonged prothrombin time	✔	-	-
Laboratory Test Abnormalities			
Creatinine phosphokinase increased	-	2.3	-
Hypoglycemia	-	3	-
Liver function test abnormalities	✔	-	✔
Triglycerides increased	-	✔	-
Musculoskeletal			
Aches	-	-	✔
Arthritis	✔	-	✔

Adverse Events	Cholestyramine	Colesevelam	Colestipol
Backache	✔	-	✔
Joint pain	-	-	✔
Muscle and joint pain	✔	-	-
Myalgia	-	2.1	-
Osteoporosis	✔	-	-
Pain	-	-	✔
Respiratory			
Nasopharyngitis	-	4.1 to 6.2	-
Pharyngitis	-	3.2	-
Rhinitis	-	2.3 to 3.2	-
Sinusitis	-	-	-
Upper respiratory tract infection	-	4.9	-
Other			
Accidental injury	-	3.7	-
Asthenia	-	3.6	-
Asthma	✔	-	-
Dental bleeding	✔	-	-
Dental caries	✔	-	-
Edema	✔	-	-
Erosion of tooth enamel	✔	-	-
Flu syndrome	-	3.2	-
Increased libido	✔	-	-
Influenza	-	3.8	-
Irritation of skin, tongue, perianal area	✔	-	-
Metabolic acidosis	✔	-	-
Rash	✔	-	✔
Shortness of breath	✔		✔
Swelling of hands or feet	-	-	✔
Swollen glands	✔	-	-
Tooth discoloration	✔	-	-
Urticaria	✔	-	✔
Uveitis	✔	-	-
Vitamin A deficiency	✔	-	-
Vitamin D deficiency	✔	-	-
Weight gain	✔	-	-
Weight loss	✔	-	-
Wheezing	✔		

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the bile acid sequestrants are listed in Table 7.

Table 7. Usual Dosing Regimens for the Bile Acid Sequestrants[2-4,14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Cholestyramine	<u>Primary hyperlipidemia:</u> Powder: initial, one packet or one level spoonful once or twice daily; maintenance, two to four packets or scoopfuls daily (8 to 16 g) divided into two doses; maximum, six packets or scoopfuls (24 g)	<u>Primary hyperlipidemia:</u> Powder: although an optimal dosage schedule has not been established, standard texts list a usual pediatric dose of 240 mg/kg/day in two to three	Powder (for oral suspension): 4 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily Relief of pruritus associated with partial biliary obstruction: Powder: initial, one packet or one level spoonful once or twice daily; maintenance, two to four packets or scoopfuls daily (8 to 16 g) divided into two doses; maximum, six packets or scoopfuls (24 g) daily	divided doses, normally not to exceed 8 g/day* Relief of pruritus associated with partial biliary obstruction: Powder: although an optimal dosage schedule has not been established, standard texts list a usual pediatric dose of 240 mg/kg/day in two to three divided doses, normally not to exceed 8 g/day*	
Colesevelam	Primary hyperlipidemia (as monotherapy or in combination with an HMG CoA reductase inhibitor): Powder: one 3.75 g packet once daily Tablet: six tablets once daily or three tablets twice daily Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Powder: 3.75 g once daily Tablet: six tablets once daily or three tablets twice daily	Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Powder: one 3.75 g packet once daily Tablet: six tablets once daily or three tablets twice daily Safety and efficacy has not been established in children <10 years of age or in premenarchal girls. Due to tablet size, the oral suspension is recommended for use in the pediatric population.	Powder (for oral suspension): 3.75 g Tablet: 625 mg
Colestipol	Primary hyperlipidemia: Granules: one to six packets or level scoopfuls given once or in divided doses; initiate treatment with one dose once or twice daily with an increment of one dose/day at one- or two-month intervals Tablet: initial, 2 g once or twice daily; maintenance, 2 to 16 g/day administered once or in divided doses	Safety and efficacy in children have not been established.	Granules (for oral suspension): 5 g (Colestid®) 7.5 g (Colestid Flavored®)† Tablet: 1 g

*The effects of long-term administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients are unknown.
†One dose contains 5 g of colestipol hydrochloride.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the bile acid sequestrants are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Bile Acid Sequestrants

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Ballantyne et al.[16] (2004) Cholestyramine 16 g/day and rosuvastatin 80 mg/day vs rosuvastatin 80 mg/day	MC, OL, PG, RCT Adults ≥18 years of age with severe hypercholesterolemia (LDL-C 190-400 mg/dL) and fasting TG <400 mg/dL	N=147 12 weeks	Primary: Percent change in LDL-C from baseline to end of treatment Secondary Percent change from baseline in LDL-C after 6 weeks of 40 mg rosuvastatin; percent change from baseline at 6 and 12 weeks of rosuvastatin treatment for: TC, HDL-C, TG, apo AI, apo B, lipid ratios (LDL:HDL) and inflammatory markers (CRP, IL6); compliance	Primary: At 12 weeks, no significant difference between the groups was seen: the rosuvastatin group had an LDL-C reduction of 56.4% and rosuvastatin with cholestyramine group had an LDL-C reduction of 60.5% (P<0.08). Secondary: LDL-C reductions were 52.2% after treatment with 40 mg rosuvastatin. Other measurements, TC, HDL-C, TG, apo B, apo AI and lipid ratios were not significantly different between the groups (P=0.20, 0.71, 0.47, 0.75, 0.53, 0.17, respectively). Decreases in CRP were 29% after 6 weeks, 42% after rosuvastatin 80 mg and 48% after rosuvastatin 80 mg with cholestyramine. 49% of patients in the cholestyramine group were not compliant with the cholestyramine treatment.
Eriksson et al.[17] (1998) Cholestyramine 16 g/day vs	MC, RCT Men and women, aged 30 to 65 years old	N=2,036 12 months	Primary: Reduction in LDL-C Secondary: Compliance	Primary: Percent change in LDL-C from baseline to end point was as follows: cholestyramine -26% (95% CI, -23 to -29), cholestyramine and pravastatin -36% (95% CI, -33 to -39), pravastatin (20 mg) -27% (95% CI, -25 to -29), pravastatin (40 mg) -32% (95% CI, -30 to -34). Secondary: Compliance rates with each regimen were as follows: cholestyramine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cholestyramine 8 g/day and pravastatin 20 mg/day vs pravastatin 20 mg/day vs pravastatin 40 mg/day				44%, cholestyramine and pravastatin 53%, pravastatin (20 mg) 76%, and pravastatin (40 mg) 78%. Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common in the cholestyramine group and the cholestyramine with pravastatin group.
Davidson et al.[18] (2010) Colesevelam 0.75 g BID, titrated up to a maximum of 1.875 g BID If a 15 to 30% LDL-C reduction was not achieved with the maximum colesevelam dose by week 12, low dose statin or niacin therapy could be added.	ES, OL Patients ≥18 years of age with primary hypercholesterolemia (LDL-C ≥160 mg/dL and TG ≤300 mg/dL)	N=260 50 weeks	Primary: Mean change from baseline in LDL-C Secondary: Mean percent change from baseline in LDL-C; mean change and mean percent change from baseline in TC, TG and HDL-C; safety	Primary: Colesevelam monotherapy or combination therapy resulted in significant mean LDL-C level reduction of 29.6 mg/dL (from 185.8 to 156.2 mg/dL), corresponding to a mean 15.0% reduction from baseline (P<0.00 for both). Secondary: Colesevelam reduced the mean TC level from baseline to week 50 (270.2 to 258.3 mg/dL) by 11.9 mg/dL (4.0%; P<0.001). The median TG level increased from baseline to week 50 (145.5 to 165.0 mg/dL) by 13.0 mg/dL (10.3%). The median HDL-C level increased from baseline to week 50 (49.5 to 54.0 mg/dL) by 5.0 mg/dL (10.8%; P<0.001). Twenty three patients discontinued colesevelam due to treatment-emergent adverse events. Treatment-emergent adverse events were reported by 225 patients (86.5%), with the majority of adverse events (74.7%) classified as mild to moderate in severity. The most common adverse events included infection (28.5%), constipation (16.5%), flatulence (13.5%) and general pain (13.1%).
Rosenson et al.[19] (2006) Colesevelam 1.5 to 3.75 g/day	DB, MC, PC, RCT Hypercholesterolemia patients, LDL-C >160 mg/dL, average age of	N=137 6 weeks	Primary: LDL particle size and LDL particle number	Primary: Mean LDL particle size increased significantly in the group receiving colesevelam 3.75 g/day (P=0.01). Mean LDL particle number decreased significantly in the group receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	56 years old		Secondary: Not reported	colesevelam 3.75 g/day by 13.7% (P=0.0002). Mean LDL particle number decreased significantly in the group receiving colesevelam 3.0 g/day by 6.8% (P=0.03). Secondary: Not reported
Bays et al.[20] (2006) Colesevelam 3.75 g/day vs placebo	MA (3 trials) Patients ≥18 years of age with LDL-C 100 mg/dL to 250 mg/dL, TG ≤300 mg/dL and on stable doses of statin therapy, either atorvastatin, pravastatin or simvastatin for ≥4 weeks	N=204 6 weeks	Primary: Mean percent change in LDL-C level from baseline to end point Secondary: HsCRP, absolute and percent change in HDL-C, TC, apo AI, apo B, TG, and absolute change in HsCRP; safety (measured by incidence of treatment-emergent adverse events)	Primary: Patients receiving colesevelam with a statin had significantly greater reductions in LDL-C than those receiving placebo plus a statin at the end of the study (P<0.01 for absolute difference; P≤0.001 for % treatment difference). Secondary: HsCRP levels decreased significantly as compared to placebo when colesevelam was combined with simvastatin or pravastatin (P=0.0154 and P=0.0279, respectively). Patients receiving colesevelam with a statin did not have a significant increase in HDL-C as compared to those receiving placebo plus a statin at the end of the study (P>0.05). Patients receiving colesevelam with a statin had significantly greater reductions in TC than those receiving placebo plus a statin at the end of the study (P<0.05). Apo B levels were not significantly different. No serious drug-related adverse events were reported. The incidence of drug-related adverse events was higher in the groups receiving colesevelam with a statin (13 to 26%) than placebo with a statin (0 to 13%).
Huijgen et al.[21] (2010) Colesevelam 3,750 mg/day	DB, PC, RCT Patients 18 to 75 years of age with familial hyper-cholesterolemia	N=86 12 weeks	Primary: Percent change from baseline to week six in LDL-C	Primary: The between-group difference in change from baseline LDL-C was significant at week six, with an least squares means change of -18.5% (95% CI, -25.3 to -11.8)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients were receiving ezetimibe/ simvastatin.	refractory to treatment		Secondary: Percentage change from weeks six to 12 in HDL-C, TC, TG, apo A1, apo B, apo B/A1; percentage change from baseline to week 12 in LDL-C; proportion of patients achieving an LDL-C target of ≤2.5 mmol/L at weeks six and 12; proportion of patients with a decrease from baseline in LDL-C ≥15% at weeks six and 12; absolute changes in fasting glucose, HbA_{1c}, and hsCRP at weeks six and 12	Secondary: Between group differences (95% CI) in LDL-C, TC, HDL-C, TG and apo B/A1 after 12 weeks were -12.0 (-17.8 to -6.3), -7.3 (-12.0 to -2.6), 3.3 (-2.4 to 9.0), 2.8 (-10.4 to 15.9) and -12.2% (-20.2 to -4.2). Mean TC concentrations were significantly reduced with colesevelam compared to placebo at weeks six and 12 (least squares means between-group differences, -11.1 and -7.3%; *P*<0.001 and *P*<0.003). On average, TG levels increased with colesevelam from baseline to weeks six and 12. There was no significant group differences in HDL-C at week six and 12 (*P* values not reported). The difference in the proportions of patients who achieved the target LDL-C (≤2.5 mmol/L) with colesevelam and placebo was not significant (9 vs 3%; *P* value not reported). The proportion of patients who achieved ≥15% reduction in LDL-C at week six was significantly higher with colesevelam (32 vs 0%; *P*<0.001). This difference remained significant at week 12 (30 vs 8%; *P*=0.012). Although not significant at week six (-0.06%), the least squares means between-group difference in change from baseline to week 12 in mean HbA_{1c} concentration was significant (-0.12%; *P*=0.027). There were no significant between-group differences in fasting glucose or hsCRP at week six and 12.
Stein et al.[22] (2010) Colesevelam 1.875 g/day vs colesevelam 3.75 g/day vs placebo	DB, PC, PG, RCT Patients 10 to 17 years of age with heFH, TC >160 mg/dL who were naïve to cholesterol lowering therapy or LDL-C >130 mg/dL who were on a statin	N=194 32 weeks	Primary: Percent change in LDL-C from baseline Secondary: Percent change in non-HDL-C, adverse events	Primary: Treatment with colesevelam 3.75 and 1.875 g/d led to a significant reduction in LDL-C (-12.5%; P<0.001) and (-6.3%; P=0.031), respectively, compared to placebo at week 8. Reductions in LDL-C were observed for statin-naïve (-10.6%; P<0.001) or statin non-naïve patients (-20.2%; P=0.031) receiving colesevelam 3.75 g/day compared to placebo. The mean change in LDL-cholesterol was -9.3% (P<0.001) from week 8 to week 26. Those who received placebo had the greatest change in mean LDL-C (-14.5%; P<0.001), followed by patients receiving 1.875 g/day (-11.6%; P<0.001) and 3.75 g/day colesevelam (-1.9%; P=0.482). Reductions in LDL-cholesterol were also observed for statin-naïve and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				statin-stable patients, and patients who either changed or added a statin. Those treated with colesevelam 3.75 g/day resulted in a mean reduction from baseline in LDL-cholesterol of -14.0% (P<0.001) across all patients. Secondary: Treatment with colesevelam 3.75 g/day resulted in a reduction in TC (-7.4%; P=0.001), non-HDL-C (-10.9%; P=0.0001), apo B (-8.3%; P=0.0009), HDL-C (6.1%; P=0.008), and apo AI (6.9%; P=0.006) at week 8. There was no significant difference in TG among the treatment groups (P=0.466). Individuals receiving colesevelam 3.75 g/day also experienced clinically significant mean reductions in TC (-8.0%; P<0.001), non-HDL-C (-11.3%; P<0.001), and apo B (-11.3%; P<0.001), clinically significant increases in mean HDL-Cl (8.1%; P<0.001) and apo AI (5.6%; P<0.001), and a median increase in triglycerides (11.5%; P<0.001) at week 32.
Insull et al.[23] (2001) Colesevelam 2.3 g vs colesevelam 3.0 g vs colesevelam 3.8 g vs colesevelam 4.5 g vs placebo	DB, MC, PC, RCT Patients with primary hypercholesterolemia, LDL-C levels between 130-220 mg/dL	N=467 32 weeks	Primary: Mean absolute change in LDL-C from baseline to the end of 24-week treatment Secondary: Mean percent change in LDL-C, mean absolute and percent change in TC, apo B, apo AI, and median absolute change and percent change in HDL-C and TG	Primary: All doses of colesevelam resulted in significant absolute and percent change decreases in LDL-C at the end point as compared to placebo (P<0.001 for all). Absolute change decreases and percent decreases in LDL-C for the 2.3, 3.0, 3.8, and 4.5 g doses were 14 (9%), 19 (12%), 24 (15%), and 28 mg/dL (18%). Secondary: All doses of colesevelam resulted in significant reductions of TC (P<0.001). Absolute change decreases and percent decreases in TC for the 2.3, 3.0, 3.8, and 4.5 g doses were 10 (4%), 15 (6%), 18 (7%) and 24 mg/dL (10%). All doses of colesevelam resulted in significant increases in HDL-C (P<0.001). Absolute changes (increases) and percent increases in TC for the 2.3, 3.0, 3.8, and 4.5 g doses were 2 (3%), 2 (4%), 2 (3%) and 2 mg/dL (3%). All doses of colesevelam resulted in significant reductions in apo B relative to baseline (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Changes in apo AI and lipoprotein did not result in significant changes relative to baseline, except the 2.3 and 3.0 g doses resulted in significant changes in apo AI (P=0.02 and 0.03, respectively) TG levels did not change significantly as compared to placebo, however increases, 5 to 10%, were seen within groups from baseline to end point (P<0.05).
Hunninghake et al.[24] (2001) Colesevelam 3.8 g vs atorvastatin 10 mg vs colesevelam 3.8 g/day and atorvastatin 10 mg/day vs atorvastatin 80 mg/day vs placebo	DB, MC, PC, RCT Patients with elevated LDL-C levels ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change in LDL-C Secondary: Change in TC, HDL-C, TG, apo B, apo AI and lipoprotein(a) from baseline	Primary: All treatment groups resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions were -12% in the colesevelam 3.8 g group, -38% in the atorvastatin 10 mg group, -48% in the colesevelam 3.8 g and atorvastatin 10 mg group and -53% for the atorvastatin 80 mg group (P<0.05, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Secondary: Colesevelam 3.8 g/day reduced TC -6% (P<0.05), increased HDL-C 3% (P<0.05), and increased TG 10%. Atorvastatin 10 mg reduced TC -27% (P<0.0001), increased HDL-C 8% (P<0.05), and reduced TG -24% (P<0.05). Colesevelam 3.8 g and atorvastatin 10 mg reduced TC -31% (P<0.0001), increased HDL-C 11% (P<0.05), and reduced TG -1%. Atorvastatin 80 mg reduced TC -39% (P<0.0001), increased HDL-C 5% (P<0.05), and reduced TG -33% (P<0.0001). Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam 3.8 g with atorvastatin 10 mg. No significant differences in HDL-C were found between the groups. Apo B levels decreased significantly for all groups relative to baseline (P<0.01). No significant changes in Apo AI and lipoprotein were reported.
Davidson et al.[25]	DB, MC, PC, RCT	N=135	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Colesevelam 2.3 g vs lovastatin 10 mg vs colesevelam 2.3 g and lovastatin 10 mg taken together vs colesevelam 2.3 g and lovastatin 10 mg taken apart vs placebo	Patients with elevated LDL-C levels	4 week	Percent change in LDL-C Secondary: Changes in TC, HDL-C, TG, apo B	Colesevelam 2.3 g and lovastatin 10 mg together significantly reduced LDL-C 34% (-60 mg/dL; P<0.0001). Colesevelam 2.3 g and lovastatin 10 mg apart significantly reduced LDL-C 32% (-53 mg/dL; P<0.0001). Lovastatin 10 mg reduced LDL-C 22% (-39 mg/dL). Colesevelam 2.3 g reduced LDL-C 7% (-13 mg/dL). Both combination treatments were more effective than either treatment alone (P<0.05). Secondary: Both combination treatments resulted in reductions in TC by 21% and apo B by 24% (P<0.0001 for each). No significant effect on HDL-C or TG was found for the combination treatments.
Knapp et al.[26] (2001) Colesevelam 2.3 g vs colesevelam 3.8 g vs simvastatin 10 mg vs	DB, MC, PC, RCT Men and women, age 18 years and older, with elevated LDL-C levels, ≥160 mg/dL and TG ≤300 mg/dL and not taking cholesterol-lowering medication	N=258 6 weeks	Primary: Change in serum LDL-C from baseline to end point Secondary: Percent change in LDL-C, mean and percent change in TC, HDL-C, TG, apo B and apo AI from baseline	Primary: LDL-C serum changes were -7 mg/dL in the placebo group, -31 mg/dL in the colesevelam 3.8 g group, -48 mg/dL in the simvastatin 10 mg group -80 mg/dL in the colesevelam 3.8 g and simvastatin 10 mg group, -17 mg/dL in the colesevelam 2.3 g group, -61 mg/dL in the simvastatin 20 mg group and -80 mg/dL for the colesevelam 2.3 g and simvastatin 20 mg group (P<0.05, P<0.0001, P<0.0001, P<0.0001, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Secondary: LDL-C percent changes were -4% in the placebo group, -16% in the colesevelam 3.8 g group,-26% in the simvastatin 10 mg group, -42% in the colesevelam 3.8 g and simvastatin 10 mg group, -8% in the colesevelam 2.3 g group, -34% in the simvastatin 20 mg group and -42% for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 20 mg vs colesevelam 3.8 g and simvastatin 10 mg vs colesevelam 2.3 g and simvastatin 20 mg vs placebo				colesevelam 2.3 g and simvastatin 20 mg group (P<0.05, P<0.0001, P<0.0001, P<0.0001, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Significant changes from baseline were found for all treatment groups in mean and percent change in TC (P<0.0001 for all except colesevelam 2.3 g for which P<0.05). Significant changes from baseline were found for mean and percent change in HDL-C for simvastatin 10 mg (P<0.05), colesevelam 3.8 g with simvastatin 10 mg (P<0.0001), colesevelam 2.3 g (P<0.05), simvastatin 20 mg (P<0.05), and colesevelam 2.3 g with simvastatin 20 mg (P<0.05). Significant changes from baseline were found for mean and percent change in TG for colesevelam 3.8 g (P<0.05), simvastatin 10 mg (P<0.05), simvastatin 20 mg (P<0.05), and colesevelam 2.3 g with simvastatin 20 mg (P<0.05). Significant reductions from baseline for apo B were found for all groups. Reductions were significant (P<0.05) compared to placebo for all treatment groups except colesevelam 2.3 g. Significant increases in apo AI were seen in all treatment groups except simvastatin 10 mg (P<0.05).
Blankernhorn et al.[27] (1987) Colestipol 30 g/day plus niacin 3 to 12 g/day vs placebo	DB, PC, RCT Nonsmoking men 49 to 59 years of age with progressive atherosclerosis who had coronary bypass surgery not involving valve replacement performed ≥3 months prior and a fasting blood cholesterol level 185 to 350 mg/dL	N=188 2 years	Primary: Coronary global change score Secondary: Change from baseline in lipid parameters	Primary: Deterioration in overall coronary status was significantly less with combination therapy compared to placebo (P<0.001). Atherosclerosis regression, as indicated by perceptible improvement in overall coronary status, occurred in 16.2 and 2.4% of patients receiving combination therapy and placebo (P=0.002). Combination therapy resulted in a significant reduction in the average number of lesions per patient that progressed (P<0.03) and the percentage of patients with new atheroma formation in native coronary arteries (P<0.03). The percentage of patients receiving combination therapy with new lesions

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P<0.04) or any adverse change in bypass grafts (P<0.03) was significant reduced. Secondary: Large, significant decreases in TC (26 vs 4%), TG (22 vs 5%), LDL-C (43 vs 5%) and LDL-C/HDL-C (57 vs 6%), and a large, significant increase in HDL-C (37 vs 2%) were achieved with combination therapy compared to placebo (P<0.001 for all). Modifications in lipid parameters achieved with combination therapy were significant compared to baseline values (P values not reported).
Brown et al.[28] (2009) Colestipol 5 to 10 g TID plus niacin 125 mg BID titrated to 1 to 1.5 g TID vs Colestipol 5 to 10 g TID plus lovastatin 20 mg BID titrated to 40 mg BID vs placebo (or colestipol if LDL-C was elevated)	DB, RCT Men ≤62 years of age with elevated apo B and a family history of CAD	N=120 32 months	Primary: Average change in the percent stenosis for the worst lesion in each of the nine proximal segments Secondary: Average changes in all lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	Primary: On average, placebo (conventional therapy) increased the index of stenosis by 2.1 percentage points a baseline of 34%. By contrast, it decreased by 0.7 percentage points with colestipol plus lovastatin and by 0.9 percentage points with colestipol and niacin (P<0.003 for trend). At trial end, on average, these nine lesions were almost 3 percentage points less severe among patients treated intensively compared to conventionally. This difference represents almost 1/10 of the amount of disease present at baseline (34% stenosis). Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease when looking at the effect of treatment on certain subsets of lesions (all lesions measured in each patient, lesions causing severe or mild stenosis and those that did not cause total occlusion at baseline). The results with both treatment groups were significantly difference from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.
Primary Prevention of Cardiovascular Events				
The Lipid Research Clinics Coronary Primary Prevention	DB, MC, RCT Asymptomatic males with primary	N=3,806 7.4 years average	Primary: CHD death and/or nonfatal MI	Primary: The cholestyramine group had a 19% reduction in risk of CHD death or nonfatal MI compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Trial[29,30] (1984) Cholestyramine vs placebo	hypercholesterolemia, following a moderate cholesterol-lowering diet		Secondary: TC and LDL-C changes, incidence rates of: positive stress tests, angina, coronary bypass surgery	Secondary The cholestyramine group had a reduction in TC of 13.4% and a reduction in LDL-C of 20.3%. The placebo group had a TC reduction of 4.9% and a LDL reduction of 7.7%. Incidence rates of positive stress tests, angina and coronary bypass surgery were decreased in the cholestyramine group by 25, 20, and 21%, respectively.
Type 2 Diabetes Mellitus				
Rosenstock et al (abstract).[31] (2010) Colesevelam 3.75 g/day vs placebo All patients received OL metformin 850 mg/day, titrated at week 2 to 1,700 mg/day.	DB, PC, RCT Adult patients with type 2 diabetes (HbA_{1c} 6.5 to 10.0%) and hyper-cholesterolemia (LDL-C ≥100 mg/dL)	N=286 16 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in LDL-C, TC, non-HDL-C, apo B, hsCRP, apo A-1 and TG; proportion of patients who achieved recommended treatment goals; safety and tolerability	Primary: Mean HbA_{1c} was reduced by 1.1 and 0.8% with colesevelam (from 7.8% at baseline to 6.6% at trial end) and placebo (from 7.5 to 6.7% at trial end), resulting in a treatment difference of -0.3% at trial end (*P*=0.0035). Secondary: Colesevelam significantly reduced LDL-C (-16.3%), TC (-6.1%), non-HDL-C (-8.3%), apo B (-8.0%) and hsCRP (-17%) (*P*<0.01 for all). Colesevelam significantly increased apo A-1 (4.4%) and TG (18.6%) compared to placebo (*P*<0.01 for all). The proportion of patients who achieved recommended goals with colesevelam compared to placebo, respectively, were as follows: HbA_{1c} <7; 67 vs 56% (*P*=0.0092), LDL-C <100 mg/dL; 48 vs 18% (*P*<0.001) and composite HbA_{1c} <7% plus LDL-C <100 mg/dL; 40 vs 12 (*P*<0.001). Safety and tolerability were similar between the two treatment groups.
Rosenson et al.[32] (2009) Colesevelam 3.75 g/day vs placebo	DB, PC, RCT Patients with type 2 diabetes who were receiving antihyperglycemic therapy (metformin, sulfonylurea, or both)	N=65 12 weeks	Primary: Effects on atherogenic lipoprotein subclasses (LDL-P, VLDL-P, IDL-P Secondary: Not reported	Primary: Colesevelam therapy was associated with a change in HbA_{1c} of -0.3% compared to a change of 0.2% in the placebo group (P=0.007). The mean percentage change in LDL-C was -9.6% in the colesevelam group compared to 2.1% in the placebo group (P=0.007). The mean percentage change in apo B was -6.3% (in the colesevelam group compared to 5.5% in the placebo group (P=0.003). There was no significant difference in TG (P=0.570) or HDL-C (P=0.585)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				among the treatment groups. The mean percent reduction in LDL-P was -15.5% (P=0.006) with colesevelam. The mean percent change of total atherogenic lipoproteins (LDL-P, IDL-P and VLDL-P) was reduced by -14.2% in colesevelam-treated patients (P=0.011 vs placebo). Secondary: Not reported
Zieve et al.[33] (2007) GLOWS Colesevelam 3.75 g/day vs placebo	DB, PC, PG, PRO, RCT Patients diagnosed with type 2 diabetes, an A1C 7.0%-10.0%, and on a stable dose of a sulfonylurea and/or metformin as their only antidiabetic agent for ≥90 days	N=65 12 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Changes in fructosamine levels, FPG levels, postprandial glucose level, meal glucose response (difference between pre and postprandial glucose levels) % change in lipids: LDL, TC, TG, apo AI and B	Primary: The change in HbA_{1c} from baseline to 12 weeks for the colesevelam group was -0.3% and for placebo 0.2%, for a treatment difference of 0.5% (P=0.007). For patients with a baseline HbA_{1c} ≥8.0, there was a greater difference in HbA_{1c}, -1.0%, after 12 weeks of treatment (P=0.002). The reduction in HbA_{1c} in the treatment groups did not differ based on oral antidiabetic treatment. Secondary: Significantly lower FPG was seen in the colesevelam group at weeks 4 and 8, (P=0.016, P=0.011), but not at week 12. Significantly lower fructosamine levels were seen in the colesevelam group at week 12 (P=0.011). Significantly lower postprandial glucose levels were seen in the colesevelam group at week 12 (P=0.026). No significant difference was seen in meal glucose response (P=0.195). Significantly lower lipid parameters, including LDL, TC, apo B and LDL particle concentration, were seen in the colesevelam group as compared to placebo (P=0.007, P=0.019, P=0.003, and P=0.037, respectively).
Bays et al.[34] (2008)	DB, PC, PG	N=316	Primary: Mean change from	Primary: Colesevelam reduced mean HbA_{1c} by 0.39% compared to a 0.15%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Colesevelam 3.75 g/day vs placebo	Patients aged 18-75 years with inadequately controlled type 2 diabetes mellitus taking a stable dose of metformin monotherapy or metformin in combination with other oral anti-diabetic medications (sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and/or meglitinides)	26 weeks	baseline in HbA_{1c} level Secondary: Mean change in HbA_{1c}, FPG, fructosamine levels, reduction in FPG >30 mg/dL or HbA_{1c} >0.7%, C-peptide, adiponectin, insulin levels, TC, LDL-C, HDL-C, non–HDL-C, TG, apo AI, apo B, TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, apo B:apo AI, hsCRP	increase with placebo (P<001). The treatment difference was observed as early as week 6 (P<001). Secondary: Colesevelam added to metformin monotherapy reduced HbA_{1c} by -0.44% compared to an increase of 0.02% with placebo (P=0.002). Colesevelam added to metformin in combination with other oral anti-diabetic drugs reduced HbA_{1c} by -0.35% compared to an increase of 0.27% with placebo (P<001). Colesevelam reduced FPG compared to placebo (-13.9 mg/dL; P=0.01), with a significant treatment difference observed at week 6 (-20.8 mg/dL; P<001). Colesevelam reduced fructosamine level compared to placebo (-23.2 μmol/L; P<0.001), with a significant treatment difference reported by 6 weeks (-25.5 μmol/L; P<0.001). Altogether, 47.7% of patients in the colesevelam group and 35.5% of patients in the placebo group experienced either a reduction in FPG >30 mg/dL or HbA_{1c} >0.7% (P=0.03). A greater percentage of patients in the colesevelam group compared to placebo achieved a reduction in HbA_{1c} >0.7% (38.3 vs 20.4%, respectively; P<0.001). Colesevelam did not produce a significant treatment difference for C-peptide compared to placebo (-0.1 ng/mL; P=0.54). Colesevelam was not associated with a significant treatment difference in adiponectin (-0.3 μg/mL; P=0.52), insulin (-0.9 μIU/mL; P=0.51), or the HOMA index (-0.3; P=0.68). Compared to placebo, colesevelam reduced LDL-C, TC, non–HDL-C, and apo B levels (P<0.001 for all). There was no significant difference in HDL-C, TG or apo AI between the treatment groups. Treatment with colesevelam led to a greater reduction in hsCRP compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to placebo (-14.4%; P=0.02).
Fonseca et al.[35](2008) Colesevelam 3.75 g/day vs placebo	DB, PC, PG Adults with type 2 diabetes mellitus that were inadequately controlled on a stable dose of sulfonylurea alone or in combination with additional oral antidiabetes agents for at least 90 days	N=461 26 weeks	Primary: Mean change in HbA_{1c} Secondary: FPG, fructosamine, C-peptide, mean change in A1C for the sulfonylurea monotherapy and sulfonylurea combination therapy cohorts; percentage of patients achieving a reduction in FPG ≥30 mg/dl or A1C ≥0.7%; lipids, lipoproteins, and lipid and lipoprotein ratios; high-sensitivity C-reactive protein (hsCRP)	Primary: Colesevelam reduced HbA_{1c} by -0.32%, whereas placebo increased A1C by 0.23% (P<0.001). Secondary: Colesevelam significantly lowered FPG compared to placebo (-13.5 mg/dl; P<0.009), with a difference observed as early as 6 weeks (-13.7 mg/dl; P<0.001). A significant difference in fructosamine was reported with colesevelam compared to placebo (-21.4 µmol/l; P<0.001). There was no significant difference in C-peptide among the treatment groups (P=0.102). A similar effect on HbA_{1c} was observed in the sulfonylurea monotherapy group (-0.79%; P<0.001) and the sulfonylurea combination therapy (-0.42%; P<0.001) groups. A significantly greater percentage of patients in the colesevelam group achieved an HbA_{1c} reduction ≥0.7% compared to placebo (35.2 vs 16.5%, respectively; P<0.001). There was a significantly greater number of individuals in the colesevelam group who achieved either a reduction in HbA_{1c} ≥0.7% or a reduction in FPG ≥30 mg/dl compared to placebo (47.5 vs 32.1%, respectively; P=0.001). Significant treatment differences in LDL-C, non–HDL-C, TC, TG, apo AI, and apo B were observed after 26 weeks of treatment with colesevelam compared to placebo (P<0.001 for all). The least squares mean percent change in LDL-C from baseline to week 26 (LOCF) was -16.1% in the colesevelam group and 0.6% in the placebo group (-16.7%; P<0.001). There was no significant difference in HDL-C among the treatment groups (P=0.916). Significant treatment differences between colesevelam and placebo were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported in TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, and apo B:apo AI (P≤0.003 for all). There was no significant difference in hsCRP among the treatment groups (P=0.063).
Goldberg et al.[36] (2008) Colesevelam 3.75 g/day vs placebo	DB, MC, PC, PG, PRO Patients 18 to 75 years of age with type 2 diabetes not adequately controlled with insulin alone or in combination with oral antidiabetes agents (a biguanide, a biguanide sulfonylurea combination, a sulfonylurea, a thiazolidinedione, or a meglitinide)	N=287 16 Weeks	Primary: Mean change in HbA_{1c} Secondary: FPG, fructosamine, HbA_{1c}, percentage of patients achieving a reduction in FPG ≥30 mg/dl or HbA_{1c} ≥0.7%, C-peptide, TC, LDL-C, HDL-C, non–HDL-C, TG, apo AI, apo B, TC:HDL-C, LDL-C:HDL-C, non–HDL-C:HDL-C, apo B:apo AI, hsCRP	Primary: The mean change in the HbA_{1c} was -0.41% in the colesevelam group and 0.09% in the placebo group (P<.001). Secondary: There was no significant difference in FPG among the treatment groups (P=0.08). Colesevelam significantly decreased mean fructosamine levels compared to placebo (P<0.001). Approximately 48.6% of patients in the colesevelam group and 31.6% of patients in the placebo group had a reduction in the FPG level >30 mg/dL or a reduction in the HbA_{1c} of >0.7% (P=0.004). More than twice as many patients in the colesevelam-treated group had a reduction in the HbA_{1c} level of 0.7% or greater compared to those in the placebo group (34.7% vs 14.0%; P<001). However, no significant difference was noted in the percentage of individuals achieving a reduction in FPG level of 30 mg/dL or higher between the colesevelam treated and placebo groups at week 16. Mean change from baseline in C-peptide levels was similar in both groups. No significant least squares mean treatment difference was evident at week 16 LOCF (P=0.65). Colesevelam resulted in a significantly greater percentage reduction in LDL-C compared to placebo (P<0.001). The median percent change and median change in triglycerides for the colesevelam and placebo groups were 22.7 vs 0.3% and 32.0 vs -1.3 mg/dL, respectively (P<0.001 for both). Treatment with colesevelam significantly reduced apo B levels by 5.3% compared to placebo (P=0.04), but did not result in a significant increase in apo AI. Colesevelam led to a significant decrease in LDL-C:HDL-C and apo B:apo AI, but not in the TC:HDL-C or non– HDL-C:HDL-C.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in hsCRP among the treatment groups (P=0.13).
Goldfine et al.[37] (2010) Colesevelam 3.75 g/day vs placebo	ES, OL Patients 18 to 75 years of age with type 2 diabetes who were inadequately controlled on insulin-based therapy, metformin-based therapy or sulfonylurea-based therapy	N=509 52 weeks	Primary: Safety and tolerability Secondary: Change in HbA_{1c} and FPG, percent change in lipid and lipoprotein levels, change in lipid ratios, percentage of patients who achieved either a reduction in HbA_{1c} ≥0.7% or FPG ≥30 mg/dL, percentage of patients who achieved HbA_{1c} <7.0%	Primary: During the extension, 70.9% of patients experienced an adverse event. The majority (88.1%) were mild or moderate in severity. Fifty-six patients (11%) experienced a drug-related adverse event. Most drug-related adverse events were gastrointestinal (constipation and flatulence) in nature. Thirty five (6.9%) discontinued use due to an adverse event; 16 patients (3.1%) discontinued due to a drug-related adverse event. Fifty-four patients (10.6%) had a serious adverse drug reaction; only one was considered to be drug related; 12 patients (2.4%) discontinued the drug due to a serious event. Seventeen patients (3.3%) reported an episode of hypoglycemia; most were considered mild and two were considered moderate severity. Secondary: Treatment with colesevelam reduced the HbA_{1c} by -0.6% compared to -0.1% with placebo. At week 52, 14.1% of patients achieved HbA_{1c} <7.0% and 26.9% of patients had a reduction in HbA_{1c} of ≥0.7%. One-hundred-twenty-six patients (24.8%) achieved a reduction in FPG ≥30 mg/dl from baseline A at 52 weeks. Improvements in mean LDL-C with colesevelam were maintained. Both groups that received colesevelam had sustained effects over time. Baseline A had lipid and lipoprotein levels were nearly the same between colesevelam and placebo. By the conclusion of the double-masked study (baseline B), the individuals that received colesevelam had reduced mean levels of LDL-C, non-HDL-C, TC, and apo B, and increased mean levels of HDL-C, median levels of TG, and mean levels of apo AI relative to baseline (baseline A). For those who received colesevelam in the double-masked study, the lipid effects were maintained through the extension. For those who received colesevelam in the 52-week extension, mean LDL-C, non-HDL-C, TC and apo B levels decreased while mean HDL-C, median TG, and mean apo A-I levels increased.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Jialal et al.[38] (2009) Colesevelam 3.75 g/day vs placebo	DB, PC, RCT (Pooled analysis of 3 trials) Patients 18 to 75 years of age with type 2 diabetes who were inadequately controlled on insulin-based therapy, metformin-based therapy or sulfonylurea-based therapy	N=1,018 16 to 26 weeks	Primary: Glycemic and lipid effects Secondary: Lipid effects on those patients on concomitant statin treatment	Primary: Mean HbA_{1c} was significantly reduced with colesevelam compared to placebo (-0.54%; P<0.0001). Mean FPG was significantly reduced with colesevelam vs placebo (-15.1 mg/dL; P<0.0001). Colesevelam therapy resulted in a significant reduction in TC and LDL-C compared to placebo (-5.15 and -15.3%, respectively; P<0.0001). TG was significantly increased in the colesevelam group relative to placebo (15.0%; P<0.0001). Non-HDL-C and apo B were reduced with colesevelam vs placebo (-6.80 and -6.6%, respectively; P<0.0001). There was no significant effect on HDL-C between the two groups. Apo AI levels increased significantly in the colesevelam group relative to placebo (2.8%; P<0.0001). Median levels of hsCRP were significantly reduced with colesevelam relative to placebo treatment (-0.4 mg/L; P=0.0009). Secondary: Colesevelam treatment resulted in a significant decrease in HbA_{1c} (-0.45%; P<0.0001) and LDL-C (-15.6%; P<0.0001) in patients on statin therapy at baseline.
Bays (abstract).[39] (2011) Colesevelam 3.75 g/day vs placebo	Post hoc analysis of 3 DB, PC, RCT Patients with type 2 diabetes receiving metformin, sulfonylurea, or insulin monotherapy or combination therapy as part of their background therapy	N=696 26 weeks	Primary: Change in baseline HbA_{1c}, change in baseline lipid parameters Secondary: Safety	Primary: Compared to placebo, colesevelam significantly reduced HbA_{1c} and FPG (mean treatment difference, -0.5% and -15.7 mg/dL, respectively; *P*<0.001 for both). Compared to placebo, colesevelam significantly reduced LDL-C (mean treatment difference, -16.5%), TC (-5.8%), non-HDL-C (-8.2%), and apo B (-7.6%) (P<0.0001 for all). Median TG levels (median treatment difference, 12.8%; P<0.0001) and mean apo AI levels (mean treatment difference, 3.3%; P<0.0001) were increased with colesevelam. There was an increase in HDL-C with colesevelam, compared to placebo, that was not significant (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Colesevelam was generally well tolerated.
Aggarwal et al.[40] (2012) Colesevelam vs placebo	MA (8 clinical trials) Patients with type 2 diabetes	N=1,038 Duration not specified	Primary: Change in baseline FPG, HbA_{1c}, LDL-C, HDL-C, TG, and TC Secondary: Not reported	Primary: Compared to placebo, there was a significant reduction in FPG with colesevelam (OR, -0.302; 95% CI, -0.448 to -0.156). Compared to placebo, there was a significant reduction in HbA_{1c} with colesevelam (OR, -0.594; 95% CI, -0.747 to -0.442). Compared to placebo, there was a significant reduction in LDL-C with colesevelam (OR, -1.346; 95% CI, -2.411 to -0.279). Compared to placebo, there was an insignificant reduction in TC with colesevelam (OR, -0.487; 95% CI, -1.641 to 0.667). Compared to placebo, there was a significant increase in TG with colesevelam (OR, -0.300; 95% CI, 0.0130 to 0.587). Secondary: Not reported
Rigby et al.[41] (2010) Rosiglitazone 4 mg/day (QD or BID) and metformin (existing therapy) vs sitagliptin 100 mg QD and metformin (existing therapy) vs	OL Patients 18 to 80 years of age with type 2 diabetes mellitus who had inadequate glycemic control (HbA_{1c} 6.5% to 10.0% on a stable regimen of metformin (1,500-2,550 mg daily), with LDL-C ≥60 mg/dL and TGs <500 mg/dL	N=169 16 weeks	Primary: Change in HbA_{1c} from baseline to week 16 Secondary: Change in HbA_{1c} from baseline to week eight, change in FPG and fasting insulin from baseline to weeks 8 and 16, change in 2-hour PPG and postprandial insulin after a meal	Primary: At week 16, HbA_{1c} was reduced from baseline in all treatment groups (LS mean change from baseline): colesevelam -0.3% (95% CI, -0.52 to -0.02; P=0.031); rosiglitazone -0.6% (95% CI, -0.83 to -0.32; P<0.001); sitagliptin -0.4% (95% CI, -0.64 to -0.13; P=0.009). Secondary: At week eight, HbA_{1c} was reduced from baseline with colesevelam and sitagliptin (-0.3%; P=0.006 and -0.5%; P<0.001, respectively), but not with rosiglitazone (-0.2%; P=0.109). FPG was significantly reduced from baseline at week eight and week 16 in all treatment groups. The two-hour PPG levels were significantly reduced from baseline at week 16 in all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
colesevelam 3.75 g/day (QD or BID) and metformin (existing therapy)			tolerance test, change in lipid parameters, percentage of participants who achieved an HbA_{1c} reduction >0.7% from baseline, percentage of participants who achieved HbA_{1c} <7.0%	There was no significant change in fasting insulin or 2-hour postprandial insulin from baseline to week 16 in any treatment group. Insulin resistance did not change with colesevelam or sitagliptin; however, there was a significant reduction with rosiglitazone from baseline to week 16 (P=0.008). LDL-C was significantly reduced from baseline with colesevelam (-11.6%; P=0.001), but was significantly increased with both rosiglitazone (7.8%; P=0.040) and sitagliptin (7.7%; P=0.011). TC levels were unchanged from baseline with colesevelam and sitagliptin; however, they were significantly increased with rosiglitazone from baseline to week 16 (P=0.006). Non-HDL-C levels were unchanged with colesevelam; however, they were significantly increased with rosiglitazone (P=0.001) and sitagliptin (P=0.029). Median TG levels increased significantly from baseline with colesevelam (P<0.00l) and rosiglitazone (P<0.00l); however, sitagliptin did not significantly affect TG levels. HDL-C levels did not change significantly from baseline with any treatment. At week 16, 23.2% of patients in the colesevelam group, 48.l % of patients in the rosiglitazone group, and 34.5% of patients in the sitagliptin group achieved a reduction in HbA_{1c} of 0.7% or greater from baseline. In addition, 10 patients in the colesevelam group, 19 in the rosiglitazone group, and 15 in the sitagliptin group achieved HbA_{1c} <7.0%. The percentages of patients who had an adverse event were 61.4% in the colesevelam group, 46.4% in the rosiglitazone group, and 48.2% in the sitagliptin group. Most of the adverse events were mild to moderate in severity.

Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial
Miscellaneous abbreviations: apo=apolipoprotein, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, CRP=C-reactive protein, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, heFH=heterozygous familial hypercholesterolemia, HOMA=homeostasis model assessment, hsCRP=high-sensitivity C-reactive protein, IDL-P=intermediate-density lipoprotein particle, IL6=interleukin 6, LDL-C=low density lipoprotein cholesterol, LDL-P=low density lipoprotein particle, LOCF=last observation carried forward, MI=myocardial infarction, TC=total cholesterol, TG=triglycerides, VLDL-C=very low density lipoprotein cholesterol

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Bile Acid Sequestrants

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cholestyramine	packet for oral suspension, powder for oral suspension	Questran®*†, Questran Light®*‡	$$$$$	$$
Colesevelam	packet for oral suspension, tablet	Welchol®	$$$$$	N/A
Colestipol	granules for oral suspension, packet for oral suspension, tablet	Colestid®*	$-$$$$$	$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The bile acid sequestrants are approved as an adjunct to diet and exercise to reduce total cholesterol and low-density lipoprotein cholesterol (LDL-C). In addition, cholestyramine is indicated to relieve pruritus associated with partial biliary obstruction.[2-4,14] Colesevelam is also indicated for the treatment of type 2 diabetes mellitus. Bile acid sequestrants can lower LDL-C by 15 to 30% and raise high-density lipoprotein cholesterol (HDL-C) by 3 to 5%. Serum triglyceride levels may increase or remain unchanged.[1] Cholestyramine (regular and light) and colestipol are available in a generic formulation.

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease or coronary heart disease equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant, niacin, or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy.[1,5-10]

Pruritus is a complication of primary biliary cirrhosis and bile acid sequestrants are the drug of choice for the treatment of this complication.[12] With regards to the use of bile acid sequestrants in the management of patients with type 2 diabetes, the American Association of Clinical Endocrinologists/American College of Endocrinology algorithm, notes that colesevelam, reduces blood glucose levels in patient with type 2 diabetes, especially in patients not adequately controlled with metformin, a sulfonylurea, or insulin [13] Guidelines do not give preference to one bile acid sequestrant over another.[1,5-13]

Clinical trials have demonstrated that the bile acid sequestrants can effectively lower LDL-C, non-HDL-C, total cholesterol and positively impact other lipid/lipoprotein parameters.[16-41] There are few trials that directly compare the efficacy and safety of these agents. Treatment with cholestyramine led to a 19% reduction in the risk of fatal and non-fatal myocardial infarction in the Lipid Research Clinics Coronary Primary Prevention Trial.[29,30] Positive cardiovascular outcomes have also been detected in clinical trials which combined bile acid sequestrants with other lipid-modifying drugs.[1] The efficacy of colesevelam as monotherapy for the treatment of type 2 diabetes has not been assessed. Furthermore, the efficacy of combination therapy with colesevelam and a DPP-4 inhibitor and a thiazolidinediones has not been and has not been extensively evaluated for the treatment of type 2 diabetes.[3] When added to existing diabetic regimens, colesevelam lowered the glycosylated hemoglobin by 0.3 to 0.6% compared to the addition of placebo.[33-41]

There is insufficient evidence to support that one brand bile acid sequestrant is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand bile acid sequestrants within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand bile acid sequestrant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cholesterol Absorption Inhibitors
AHFS Class 240605
February 13, 2013

I. Overview

The antilipemic agents are categorized into five different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins) and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration-approved indications, mechanism of action, efficacy, safety profiles, tolerability and ease of use.

Ezetimibe is the only cholesterol absorption inhibitor that is currently available. It inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe can lower low-density lipoprotein cholesterol by about 18%.[1]

The cholesterol absorption inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ezetimibe is not available in a generic formulation. This class was last reviewed in August 2010.

Table 1. Cholesterol Absorption Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ezetimibe	tablet	Zetia®	none

PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cholesterol absorption inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cholesterol Absorption Inhibitors

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[2] (2004)**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals.

Clinical Guideline	Recommendation
	• Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report[3] (2002)**	<u>General recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Statins</u> • Statins should be considered as first-line drugs when LDL-lowering

Clinical Guideline	Recommendation
	drugs are indicated to achieve LDL treatment goals. <u>Bile acid sequestrants</u> • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. <u>Nicotinic acid</u> • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <u>Fibric acid derivatives (fibrates)</u> • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <u>Omega-3 fatty acids</u> • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.

Clinical Guideline	Recommendation
American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update[4] (2011)**	<u>Lipid management</u> • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults[5] (2011)**	<u>Clinical highlights</u> • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures. • Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established coronary artery disease, non-cardiac atherosclerosis, or coronary artery disease equivalent. <u>Ongoing drug therapy</u> • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not

Clinical Guideline	Recommendation
	shown a decrease in mortality, although most have shown about a 30% reduction in CHD events. <u>Monotherapy</u> • Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy. • Specific statin and dose should be selected based on cost and amount of lipid-lowering required. • If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. • Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. • Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc). • Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin. • Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate). • Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease. • The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin. • The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown. • Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks.

Clinical Guideline	Recommendation

	Bile acid sequestrants are good for combination therapy and are most potent with a statin.
	• Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after.
	
	Combination therapy
	• It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe.
	  o A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy.
	  o No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events.
	  o The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints.
	• Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy.
	• Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit.
	• There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins.
	• No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy.
	
	Lifestyle modifications
	• Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss.
	• Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range.
	• A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended.
	• Vitamin E supplementation should not be used.
	• Light to moderate consumption of alcohol may lower CHD rates.
	• Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).

American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association[6] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired

Clinical Guideline	Recommendation
	target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice[7] (2012)**	<u>Drugs</u> • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. • Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. • Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. <u>Drug combinations</u> • Patients with dyslipidemia, particularly those with established CVD, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
National Institute for Health and Clinical Excellence:	• Statin therapy is recommended as part of the management strategy for the primary prevention of cardiovascular disease for adults who have a

Clinical Guideline	Recommendation
Lipid Modification[8] (2010)	≥20% 10 year risk of developing cardiovascular disease. • Treatment for the primary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of cardiovascular disease. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of cardiovascular disease. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of cardiovascular disease. • Statin therapy is recommended for adults with clinical evidence of cardiovascular disease. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dL) or LDL-C <2 mmol/L (<77 mg/dL) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with cardiovascular disease who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[9] (2011)**	• Risk factor control for all patients with transient ischemic attack (TIA) or ischemic stroke: • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD. • For patients with atherosclerotic ischemic stroke or TIA without known CHD, it is reasonable to target a reduction of ≥50% in LDL-C or a target LDL-C level <70 mg/dL to obtain maximal benefit. • Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to the National Cholesterol Education Program III guidelines (i.e., lifestyle modification, dietary guidelines, medication recommendations). • Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cholesterol absorption inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Cholesterol Absorption Inhibitors[1]

Indication	Ezetimibe
Adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patient with homozygous familial sitosterolemia	✔
Adjunctive therapy to diet for the reduction of elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with primary hyperlipidemia	✔
Administered in combination with a HMG-CoA reductase inhibitor (statin), as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, apo B, and non-HDL-C in patients with primary hyperlipidemia	✔
Administered in combination with fenofibrate, as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, apo B, and non-HDL-C in adult patients with mixed hyperlipidemia	✔
Administered in combination with simvastatin or atorvastatin for the reduction of elevated TC and LDL-C levels in patient with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the cholesterol absorption inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Cholesterol Absorption Inhibitors[10]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ezetimibe	Not reported	>90	Intestine (extensive; % not reported); Liver (% not reported)	Renal (11) Feces (78)	19 to 30

V. Drug Interactions

Significant drug interactions with the cholesterol absorption inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the Cholesterol Absorption Inhibitors[11]

Generic Name(s)	Significance Level	Interaction	Mechanism
Ezetimibe	2	Cyclosporine	Although the mechanism is unknown, when cyclosporine and ezetimibe are administered concomitantly exposure to both drugs may be increased, potentially increasing the pharmacologic effects and adverse reactions.

Significance Level 1 = major severity.
Significance Level 2 = moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the cholesterol absorption inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Cholesterol Absorption Inhibitors[1]

Adverse Events	Ezetimibe
Central Nervous System	
Depression	✔
Dizziness	✔
Fatigue	1.6 to 2.4
Headache	✔
Paresthesia	✔

Adverse Events	Ezetimibe
Dermatologic	
Erythema multiforme	✔
Rash	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain	✔
Diarrhea	2.2 to 4.1
Nausea	✔
Hematologic	
Thrombocytopenia	✔
Laboratory Test Abnormalities	
Creatine phosphokinase increased	✔
Liver transaminases increased	1
Musculoskeletal	
Arthralgia	2.4 to 3.0
Back pain	2.3
Myalgia	3.2 to 3.7
Myopathy	✔
Pain in extremities	1.9 to 2.7
Rhabdomyolysis	✔
Respiratory	
Coughing	2.3
Nasopharyngitis	3.3 to 3.7
Sinusitis	2.8
Upper respiratory tract infection	2.8 to 4.3
Other	
Anaphylaxis	✔
Angioedema	✔
Cholecystitis	✔
Cholelithiasis	✔
Hepatitis	✔
Hypersensitivity reactions	✔
Influenza	2.0 to 2.1
Pancreatitis	✔

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the cholesterol absorption inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Cholesterol Absorption Inhibitors[1]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ezetimibe	<u>Homozygous familial hypercholesterolemia:</u> Tablet: 10 mg once daily <u>Homozygous sitosterolemia:</u> Tablet: 10 mg once daily <u>Primary hypercholesterolemia:</u> Tablet: 10 mg	<u>Heterozygous familial hypercholesterolemia in children ≥10 years of age:</u> 10 mg once daily Safety and efficacy in children <10 years of age and in premenarchal girls have not been established.	Tablet: 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cholesterol absorption inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Cholesterol Absorption Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Pearson et al.[12] (2006) Ezetimibe 10 mg QD Patients either received ezetimibe as monotherapy, in combination with a low-dose statin (20 mg/day or less of atorvastatin or its equivalent), or in combination with a high-dose statin (20 mg/day or more of atorvastatin or its equivalent).	Cohort, RETRO Men and women ≥18 years old who took ezetimibe for a minimum of two weeks	N=84 2 to 6 weeks	Primary: Change in fasting lipid profile at baseline to 2 to 6 weeks of ezetimibe therapy, clinical effectiveness results stratified by primary vs secondary prevention Secondary: Percentage of patients able to achieve their LDL-C target levels in accordance with their calculated Framingham risk category and defined Canadian guidelines and safety and tolerability	Primary: The mean reductions from baseline to two to six weeks of ezetimibe therapy were: TC 1.11mmol/L (16.5%), LDL-C level 1.01 mmol/L (22.3%), and ratio of TC:HDL 0.68 mmol/L (12.8%) (P<0.001 for all). The HDL-C level increased by 0.06 mmol/L (4.6%) from baseline to two to six weeks of ezetimibe therapy (P<0.001). Results were similar when stratified by primary (n=28) vs secondary (n=56) prevention. Among the primary prevention group, only the TC levels, LDL-C levels and TC:HDL ratio reductions were statistically significant (P<0.001). In the secondary prevention group, the reductions in TC levels, LDL-C levels, HDL-C levels and TC:HDL ratio all achieved statistical significance (P<0.001). LDL-C level reductions from baseline, stratified by drug regimen, were -1.03 mmol/L (-20.5%) for ezetimibe monotherapy, -1.19 mmol/L (-30.1%) for ezetimibe and a low-dose statin, and -0.95 mmol/L (-22.5%) for ezetimibe plus a high-dose statin (P<0.001 for ezetimibe monotherapy and ezetimibe plus a high-dose statin; P=0.0017 for ezetimibe plus a low-dose statin). Secondary: There were seven patients out of 34 (20.6%) in the ezetimibe monotherapy group, five out of 12 (41.6%) in the ezetimibe plus low-dose statin group and 18 out of 38 (47.4%) in the ezetimibe plus high-dose statin group who achieved previously unattainable target LDL-C levels. There were four patients who discontinued therapy due to treatment-related adverse event.
Jelesoff et al.[13] (2006) Ezetimibe 10	RETRO Patients who received ezetimibe as add-on	N=53 Not reported	Primary: TC, LDL-C, TG, HDL-C	Primary: The addition of ezetimibe resulted in reductions of 18, 25, and 17% (P<0.001) for TC, LDL-C, and TG, respectively. There were no significant differences in HDL-C (P value not significant).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day All patients were receiving niacin.	therapy to stable doses of niacin and other lipid medications		Secondary: Percent change in patients meeting NCEP ATP III treatment guidelines	Secondary: Thirteen percent of patients met goals prior to addition of ezetimibe while 45% of patients met goals following addition of ezetimibe (P<0.001).
Simons et al.[14] (2007) EASY Ezetimibe 10 mg QD All patients were receiving statin therapy.	OL Men and women from Australia, mean age 65.6 years, with CHD or diabetes mellitus who had already used ≥40 mg/day of a statin for ≥3 months with current TC of >4 mmol/L for existing CHD or >6.5 mmol/L for diabetes or >5.5 mmol/L for diabetes if HDL-C is <1.0 mmol/L	N=130 6 weeks	Primary: LDL reduction and percentage of patients who reached LDL goal of <2.5 mmol/L or <2.0 mmol/L and other lipid parameters Secondary: Not reported	Primary: The LDL-C levels after six weeks were reduced by 29% (95% CI, 25 to 34) in patients receiving ezetimibe. Goal LDL-C of <2.5 and <2.0 mmol/L were reached by 70 and 50% of patients receiving ezetimibe (95% CI, 59 to 79 and 39 to 60, respectively). TC and TG levels were reduced by 19 and 11%, respectively, in patients receiving ezetimibe (95% CI, -21 to -16 and -16 to -5). There were no significant changes in HDL-C observed (95% CI, 0 to 6). Secondary: Not reported
Bissonnette et al.[15] (2006) Ezetimibe 10 mg QD All patients were receiving statin therapy.	MC, OL, PRO Men and women ≥18 years of age with a confirmed diagnoses of hypercholesterolemia and elevated plasma LDL-C levels of ≥2.5 mmol/L for patients at high 10-year CAD risk, ≥3.5 mmol/L for patients at moderate 10-year CAD risk and ≥4.5 mmol/L for patients at low 10-year	N=953 6 weeks	Primary: Percentage of change in LDL-C during the 6 week treatment period Secondary: Percentage of patients who had achieved the recommended target LDL-C levels at the end of the 6 week treatment period	Primary: After six weeks of treatment with ezetimibe, a statistically significant mean reduction was observed in LDL-C (30.5%; P<0.001). Secondary: At six weeks, 674 patients (80.5%) achieved the recommended target LDL-C levels. After six weeks of treatment with ezetimibe, statistically significant mean reductions were observed in TC (20.8%), TG (10.1%), apo B (19.8%), and TC:HDL ratio (19.9%) (P<0.001). There were 50 mild, nonserious adverse events related to ezetimibe reported by 32 patients (3.4%). Frequently reported adverse events included constipation (0.7%), diarrhea (0.4%) and dizziness (0.4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	CAD risk category, on a stable diet and statin regimen for ≥4 weeks before study entry		and the percentage of change in TC, TG, HDL-C, apo B and the TC:HDL-C ratio, safety and tolerability	
Pitsavos et al.[16] (2009) Ezetimibe 10 mg QD All patients were receiving high-dose statin therapy.	OL Patients with heFH who were receiving treatment with high-dose statins (atorvastatin 80 mg, pravastatin 40 mg, rosuvastatin 40 mg, simvastatin 80 mg, fluvastatin 80 mg)	N=70 12 months	Primary: Lipid and lipoprotein parameters Secondary: Not reported	Primary: After three months, treatment with ezetimibe led to a significant reduction in TC (P<0.05), LDL-C (P<0.05), TG (P<0.05) and apo B (P<0.05), which persisted until 12 months. There were no significant changes in HDL-C, apoA, Lp(a), fibrinogen, or hsCRP with ezetimibe. Secondary: Not reported
Strony et al.[17] (2008) Ezetimibe 10 mg QD coadministered with either pravastatin 10 to 40 mg QD or simvastatin 10 to 80 mg QD	Pooled analysis of 2 ES, MC, OL Patients with primary hypercholesterolemia	N=795 12 to 15 months	Primary: Tolerability Secondary: LDL-C, HDL-C, TG, TC, and proportion of patients achieving LDL-C goal	Primary: Treatment-emergent adverse events were reported in 81% of patients receiving ezetimibe plus pravastatin (15 months) and in 84% of patients receiving ezetimibe plus simvastatin (12 months). The most commonly reported treatment-emergent adverse events were upper respiratory tract infection (18%), headache (11%), musculoskeletal pain (10%), arthralgia (10%), sinusitis (10%), abdominal pain (8%), bronchitis (6%), coughing (6%), nausea (6%), back pain (5%), myalgia (5%), chest pain (5%), and fatigue (5%) with ezetimibe plus pravastatin. The most commonly reported treatment-emergent adverse events were upper respiratory tract infection (19%), arthralgia (11 %), musculoskeletal pain (10%), headache (9%), back pain (8%), myalgia (8%), abdominal pain (7%), nausea (7%), pharyngitis (6%), coughing (5%), fatigue (5%), and urinary tract infection (19%) with ezetimibe plus simvastatin. During the ezetimibe plus pravastatin extension study, 7% experienced serious adverse events. During the ezetimibe plus simvastatin extension

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				study, serious adverse events were reported in 10% of patients. Life-threatening adverse events were reported in four patients in the ezetimibe plus simvastatin study. The incidence of newly reported adverse events did not increase over time in either study. In the ezetimibe plus pravastatin study, 1% of patients experienced increases in ALT/AST >3 X upper limit of normal, whereas this was not reported in the patients receiving ezetimibe plus simvastatin. Secondary: The mean LDL-C was reduced by 36.5 and 40.4% in the ezetimibe plus pravastatin and ezetimibe plus simvastatin studies, respectively. Similar reductions in TC and TG, and an increase in HDL-C, were achieved and maintained throughout the study period in both studies. In the ezetimibe plus pravastatin study, 85% of patients achieved their NCEP ATP III LDL-C goal and 80% of patients in the ezetimibe plus simvastatin study achieved their recommended goal.
Salen et al.[18] (2004) Ezetimibe 10 mg/day vs placebo	DB, MC, PC, RCT Patients ≥10 years of age with a diagnosis of sitosterolemia who had plasma sitosterol levels >0.12 mmol/L despite current treatment	N=37 8 weeks	Primary: Percent change from baseline in sitosterol concentration Secondary: Not reported	Primary: Ezetimibe resulted in a mean percent reduction in sitosterol of 21% (P<0.001) compared to a nonsignificant increase of 4% with placebo (P value not reported). The between-group difference in mean percent change in sitosterol was -25% (95% CI, -36.7 to -13.2; P<0.001). The reduction in plasma sitosterol during the DB period was progressive beginning at week two, with greater reduction from baseline observed at each subsequent visit. Secondary: Not reported
Lutjohann et al.[19] (2008) Ezetimibe 10 mg/day	ES Patients ≥10 years of age with a diagnosis of sitosterolemia who had plasma sitosterol levels	N=21 2 years	Primary: Percent change from baseline in sitosterol concentration	Primary: Ezetimibe resulted in significant mean percent reductions in sitosterol (-43.9%; 95% CI, -52.2 to -35.6; P<0.001). Progressively larger reductions in sitosterol were observed during the first 40 weeks of the OL extension phase, with maximal reductions achieved by 52 weeks of treatment (-47.6%; 95% CI, -50.9 to -44.4; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	>0.12 mmol/L despite current treatment		Secondary: Percent change from baseline in campesterol concentration and LDL-C	Secondary: Ezetimibe resulted in significant mean reductions in campesterol (-50.8%; 95% CI, -58.8 to -42.7; P<0.001). Plasma concentrations progressively declined over the first 40 weeks of the trial reaching a maximum reduction of -53.6% (95% CI, -56.9 to -50.3) at week 52. After week 52, plasma concentrations remained generally stable for the remainder of the 104 week treatment period. Ezetimibe resulted in significant mean reductions from baseline in LDL-C (-13.1%; 95% CI, -25.0 to -1.2; P=0.032) at week 104.
Musliner et al.[20] (2008) Ezetimibe 30 mg/day vs placebo All patients continued on OL ezetimibe 10 mg/day for the duration of the trial.	DB, MC, PC, PG, RCT Patients ≥18 years of age with homozygous sitosterolemia who were taking ezetimibe 10 mg/day for ≥6 months prior to enrollment	N=27 26 weeks	Primary: Percent between-group change from baseline in sitosterol Secondary: Between-group changes in campesterol, lathosterol and achilles tendon thickness size; safety	Primary: Ezetimibe 40 mg/day resulted in a median percent change in sitosterol of 3.3 vs -10.0% with ezetimibe 10 mg/day, resulting in a between-group difference of 9.6% (P=0.180). Secondary: Median percent changes in campesterol were -9.7 vs -0.5% with ezetimibe 10 and 40 mg/day, resulting in a between-group difference of 7.6% (P=0.359). Median percent changes in lathosterol were 0.8 vs 1.1% with ezetimibe 40 and 10 mg/day, resulting in a between-group difference of 5.2% (P=0.701). Achilles tendon thickness increased slightly with ezetimibe 10 mg/day (2.2%) and remained unchanged with 40 mg/day, resulting in a nonsignificant between-group difference of -2.2% (P=0.404). Ezetimibe 40 mg/day was generally well tolerated. Laboratory safety parameters remained stable during the treatment period. No patients receiving ezetimibe in the trial experienced elevations in AST or AST greater than threefold or in creatinine kinase greater than tenfold the upper limit of normal.
Dujovne et al.[21] (2002)	DB, MC, PC, RCT Adult men and women	N=892 12 weeks	Primary: Percent change from baseline to	Primary: The ezetimibe group achieved a mean percent reduction from baseline to end point in the plasma concentration of LDL-C of 16.9% compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD vs placebo	aged ≥18 years with a diagnosis of primary hypercholesterolemia (LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout)		end point in plasma concentration of direct LDL-C Secondary: Changes and percent changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, and HDL-C at end point, changes from baseline HDL_2-C and HDL_3-C, apo AI, apo B, Lp(a) at end point, adverse events	0.4% in the placebo group (P<0.01). Secondary: There was a -17.68% compared to a 1.11% change in the calculated LDL-C from baseline in the ezetimibe and placebo groups, respectively (P<0.01). Ezetimibe also significantly decreased the apo B, TC, and TG as well as significantly increased HDL-C and HDL_3-C from baseline (P<0.01). However, there was no significant change in HDL_2-C and apo AI with ezetimibe compared to placebo (P=0.76 and P=0.50, respectively). Treatment-emergent adverse events occurred in 66% of patients taking ezetimibe and 63% of patients taking placebo. The most commonly reported adverse event in both treatment groups were upper respiratory tract infections and headache. The adverse events were considered to be mild to moderate and were similar between treatment groups.
Knopp et al.[22] (2003) Ezetimibe 10 mg QD vs placebo	DB, MC, PC, RCT Adult men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL)	N=827 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of direct LDL-C Secondary: Changes and percentage changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, HDL-C at end point, HDL_2-C,	Primary: The mean plasma concentration of direct LDL-C from baseline to end point was 17.7% in the ezetimibe group compared to 0.8% in the placebo group (P<0.01). Secondary: Ezetimibe significantly decreased calculated LDL-C, apo B, TC and Lp(a) and significantly increased HDL-C and HDL_2-C (P≤0.01 for all). However, the change in HDL_3-C, apo AI, and TG from baseline did not result in significant differences between treatment groups (P=0.49, P=0.27, P=0.09). The percentage of patients reporting treatment-emergent adverse events was 61% in the ezetimibe group and 65% in the placebo group. No individual adverse event was prevalent in either group and all were considered mild to moderate in severity. Overall, the adverse event profiles were similar between both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			HDL_3-C, apo AI, apo B, Lp(a), adverse events	
Knopp et al.[23] (2003) Ezetimibe 10 mg QD vs placebo	Pooled analysis of 2 DB, MC, PC, RCT Men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout)	N=1,719 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of LDL-C Secondary: Percentage change from baseline in TC, TG, HDL-C, HDL_2-C, HDL_3-C, apo AI, apo B, Lp(a), adverse events	Primary: In the pooled analysis, LDL-C was reduced by a mean 18.2% from baseline in the ezetimibe group compared to an increase of 0.9% in the placebo group (P<0.01). Secondary: Ezetimibe significantly decreased TC, apo B, Lp(a), and TG and increased HDL-C compared to placebo (P<0.01). However, there were no statistically significant differences in the change of HDL_2-C, HDL_3-C and apo AI between ezetimibe and placebo (P=0.08, P=0.06, and P=0.26). The overall adverse event profiles were similar between the ezetimibe and placebo groups. Approximately 62% of patients in the ezetimibe group and 62% of patients in the placebo group reported adverse events. Also, there were no significant between-group differences in the laboratory or clinical safety parameters or gastrointestinal, liver, or muscle side effects.
Wierzbicki et al.[24] (2005) Ezetimibe 10 mg QD vs placebo	PRO Patients with refractory familial hyperlipidemia or intolerance to statin therapy	N=200 Not reported	Primary: LDL-C, TG, HDL-C, CRP, ALT Secondary: Not reported	Primary: Ezetimibe was associated with 7% reductions in LDL-C and 11% reductions in apo B. The proportion of patients achieving LDL-C <3 mmol/L increased from 6 to 18%. There were no significant differences in TG, HDL-C, CRP, or ALT. Secondary: Not reported
Kalogirou et al.[25] (2007) Ezetimibe 10 mg QD vs placebo	PRO Patients with primary dyslipidemia and no evidence of CHD, average 54 years of age, average BMI of 26.9 kg/m^2	N=50 16 weeks	Primary: Lipoprotein subfractions Secondary: Not reported	Primary: A significant median reduction in serum HDL-C concentration from 1.5 mmol/L (1.1 to 2.6) at baseline to 1.4 mmol/L (0.9 to 2.6) posttreatment was observed with ezetimibe treatment. The median change in HDL-C was -6.6% (P<0.001). A significant median reduction in TC from 7.1 mmol/L (4.9 to 11.1) at baseline to 5.8 mmol/L (4.3 to 8.9) posttreatment was observed with ezetimibe treatment. The median change in TC was -15.5% (-34.5 to 4.2%) with ezetimibe

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment (P<0.001 vs placebo). Mean serum TG decreased from 1.5 mmol/L (0.6 to 4.28) at baseline to 1.4 mmol/L (0.6 to 3.2) posttreatment; a median percent change of 9.3% (-32.4 to 15.7%; P<0.05). Mean serum LDL-C levels significantly decreased from 3.8 mmol/L (2.5 to 7.3) at baseline to 3.2 mmol/L (1.8 to 5.4) posttreatment; a median percent change of –20.1% (-51.1 to 23.1%; P<0.001). Secondary: Not reported
Gonzalez-Ortiz et al.[26] (2006) Ezetimibe 10 mg QD vs placebo	DB, PC, RCT Obese, dyslipidemic patients 18 to 45 years old	N=12 90 days	Primary: TC, LDL-C Secondary: HDL-C, TG, VLDL-C	Primary: Ezetimibe-treated patients compared to placebo-treated patients had decreased TC (6.0 vs 4.2 mmol/L; P=0.011) and LDL-C (4.0 vs 2.2 mmol/L; P=0.003) without affecting insulin sensitivity. Secondary: There were no differences in HDL-C, TG, and VLDL-C (P values not significant).
Pearson et al.[27] (2005) Ezetimibe 10 mg QD vs placebo Patients in both groups continued to receive their current dose of statin therapy.	DB, MC, PC, PG Hypercholesterolemic patients ≥18 years of age with LDL-C levels exceeding NCEP ATP III goals while taking a stable, approved dose of any statin, following a cholesterol-lowering diet for ≥6 weeks	N=3,030 6 weeks	Primary: Percent reduction in LDL-C level from baseline after 6 weeks of DB treatment Secondary: Percentage of patients who achieved NCEP ATP III target LDL-C levels in the total population and by NCEP ATP III risk categories	Primary: Ezetimibe added to a statin significantly reduced mean LDL-C levels by an additional 25.8% compared to a reduction of 2.7% with the addition of placebo to statin (95% CI, -24.4 to -21.7%; P<0.001). Secondary: The addition of ezetimibe to statin resulted in an additional 23.8 to 25.7% reduction in LDL-C in all NCEP ATP III risk categories. Treatment differences were -24.0, -19.7, and -19.9% in the CHD or CHD risk equivalent, multiple risk factors, or <2 risk factors groups, respectively (P<0.001 ezetimibe vs placebo for each risk category). No significant differences were found according to age, sex, or race category (P>0.05).
Bays et al.[28] (2006)	DB, MC, PC, PG, RCT	N=86	Primary: Mean percent	Primary: After six weeks of treatment, ezetimibe produced a mean percent decrease

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD vs placebo All patients were receiving colesevelam 3.8 QD.	Men and women with primary hypercholesterolemia	4 to 8 weeks washout period and 6 weeks of treatment	change in LDL-C, mean absolute and mean percent change in HDL-C, non-HDL-C, TC, apo AI and apo B, and median absolute and percent changes in TG and hsCRP from baseline to end of treatment Secondary: Safety and tolerability	in LDL-C of 32.3 vs 21.4% with placebo (P<0.0001). Ezetimibe was significantly more effective placebo at producing mean percent reductions in TC, non-HDL-C, apo B and increases in apo AI (P<0.005 for all). Neither treatment resulted in significant changes in median TG levels compared to baseline (P value not significant). Secondary: Both treatment groups were safe and generally well tolerated.
Blagden et al.[29] (2007) Ezetimibe 10 mg QD vs placebo All patients received atorvastatin 10 mg QD.	DB, MC, PC, RCT Men and women with primary hypercholesterolemia and CHD	N=148 6 weeks	Primary: Mean percentage change in LDL-C from baseline to study end point Secondary: Percentage of patients achieving the new JBS 2 recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L, percentage of patients reaching LDL-C targets, safety and tolerability	Primary: From baseline to week six, ezetimibe and atorvastatin provided significantly greater reductions in adjusted mean LDL-C level compared to atorvastatin monotherapy, (-50.5 vs -36.5%; P<0.0001), equating to an additional 14.1% reduction (95% CI, -17.90 to -10.19). Secondary: A significantly higher proportion of patients on ezetimibe and atorvastatin achieved the new JBS 2 recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L compared to atorvastatin monotherapy (62 vs 12%; P<0.0001 and 93 vs 79%, respectively). Patients receiving ezetimibe and atorvastatin were 12 times more likely to reach LDL-C targets (OR, 12.1; 95% CI, 5.8 to 25.1; P<0.0001) compared to patients receiving atorvastatin monotherapy. Clinical chemistry profiles and the incidence of adverse events were similar in both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rodney et al.[30] (2006) Ezetimibe 10 mg QD vs placebo All patients received simvastatin 20 mg/day.	DB, MC, PC, PG, RCT African-American patients with LDL-C ≥145 mg/dL but ≤250 mg/dL, TG ≤350 mg/dL	N=247 12 weeks	Primary: Mean change from baseline in LDL-C level, total cholesterol, TG, HDL-C, non-HDL-C, apo B Secondary: Not reported	Primary: Patients receiving ezetimibe experienced a statistically significant LDL-C reduction from baseline compared to patients receiving placebo (45.6 vs 28.3%; P≤0.01). Patients receiving ezetimibe experienced a statistically significant reduction in TC from baseline compared to patients receiving placebo (33 vs 21%; P≤0.01). Patients receiving ezetimibe experienced a statistically significant TG reduction from baseline compared patients receiving placebo (22 vs 15%; P≤0.01). Patients receiving ezetimibe experienced a statistically significant non-HDL-C reduction from baseline compared to patients receiving placebo (42 vs 26%; P≤0.01). Patients receiving ezetimibe experienced a statistically significant apo B reduction from baseline compared to patients receiving placebo (38 vs 25%; P≤0.01). There was no difference in the change of HDL-C level from baseline between the two groups (~1-2% increase in each group). There was no statistically significant difference in side effects between the two groups. Secondary: Not reported
Patel et al.[31] (2006) Ezetimibe 10 mg vs placebo	DB, MC, PC, PG, RCT Men and women aged 18 to 75 years with primary hypercholesterolemia (LDL ≥3.3 mmol/L and ≤4.9 mmol/L, TG	N=153 6 weeks	Primary: Mean change in LDL-C level from baseline to 6 weeks, proportion of patients who reached an LDL-C goal of <3 mmol/L	Primary: At six weeks, patients receiving ezetimibe had a mean LDL-C reduction of 14.6% (95% CI, 10.1 to 19.1). At six weeks, a greater number of patients receiving ezetimibe reached an LDL-C goal <3 mmol/L compared to patients receiving placebo (93 vs 75%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
All patients received simvastatin.	<3.99 mmol/L) and documented CHD ≥3 months prior to baseline who were not receiving pharmacologic lipid management therapy		at end point Secondary: Changes in serum TC, TG and HDL-C levels, safety and tolerability	Secondary: At six weeks, there was a significant additional reduction in TC of 0.69 mmol/L in patients receiving ezetimibe compared to patients receiving placebo (95% CI, 0.48 to 0.90; P<0.0001). There was a 20.4% reduction in TG levels in the ezetimibe group compared to a 12.4% reduction in the placebo group (P=0.06). Baseline HDL-C levels increased by 6% in both treatment groups. In the ezetimibe group, 40% of patients had at least one treatment-emergent adverse event compared to 25% in the placebo group. The overall incidence of adverse events were not significant among the two groups (P=0.07). Two patients in the ezetimibe group and one patient in the placebo group experienced a serious adverse event unrelated to the study medications.
Landry et al.[32] (2006) Ezetimibe 10 mg QD vs placebo All patients received simvastatin.	MC, PC, RCT Men and women ≥18 years of age, patients on predialysis with creatinine level ≥1.7 mg/dL, hemodialysis, or peritoneal dialysis	N=203 6 months	Primary: LDL-C, TC, non-HDL-C, HDL-C, TG, apo B, apo AI Secondary: Tolerability and safety	Primary: Both groups had statistically reduced LDL-C at one, three, and six months compared to baseline (P<0.0001). The addition of ezetimibe to simvastatin was associated with 27, 26, and 21% reductions in LDL-C at one, three, and six months, respectively. The addition of ezetimibe to simvastatin was associated with 16, 16, and 14% reductions in TC at one, three, and six months, respectively. The addition of ezetimibe to simvastatin was associated with 24, 25, and 19% reductions in non-HDL-C at one, three, and six months, respectively. The addition of ezetimibe to simvastatin was associated with 15, 14, and 12% reductions in apo B at one, three, and six months, respectively. There were no significant effects in HDL-C, TG, or apo AI (P value not significant) except for 7% increase of HDL-C at three months (P=0.02). Secondary: There were no significant differences in muscle pain, muscle weakness, abdominal discomfort, nausea, constipation, or appetite loss between groups (P value not significant). More patients on ezetimibe reported diarrhea (27 vs 12%; P=0.009).

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				There were no significant differences in CK levels or abnormal hepatic transaminase levels.
Bays et al.[33] (2008) Ezetimibe 10 mg QD vs placebo All patients received simvastatin 80 mg QD.	ES Patients ≥18 years of age with primary hypercholesterolemia	N=768 48 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: In general, combination therapy did not substantively differ from simvastatin with respect to total adverse events (73 vs 69%), treatment related adverse events (13.5 vs 11.4%), treatment related serious adverse events (1 vs 0%), discontinuations due to treatment related adverse events (2.8 vs 2.6%) or discontinuations due to treatment-related serious adverse events (1 vs 0%). Combination therapy had a slightly higher rate of serious adverse events (5.2 vs 2.6%) and discontinuations due to adverse events (4.5 vs 2.6%) compared to simvastatin (P>0.20). Based on investigator assessment of causality, rates were similar between the treatments. There are no remarkable observations of between-treatment group differences whether or not they are related to a specific tissue or body system. In general, combination therapy did not differ from simvastatin with respect to total laboratory adverse events (12 vs 12%), treatment related laboratory adverse events (6.2 vs 5.3%), total laboratory serious adverse events (0 vs 0%), treatment related laboratory serious adverse events (0 vs 0%) or discontinuations due to laboratory serious adverse events (0 vs 0%). Secondary: Not reported
van der Graaf et al.[34] (2008) Ezetimibe 10 mg QD vs	DB, MC, PC, RCT Patients 10 to 17 years of age with heFH	N=248 53 weeks	Primary: Percent change from baseline in LDL-C after six weeks Secondary: TC, HDL-C, TG,	Primary: After six weeks of therapy, ezetimibe lowered LDL-C by -49.5% compared to -34.4% with placebo (P<0.01). Secondary: After six weeks of therapy, ezetimibe was more effective compared to placebo in lowering TC (-38.2 vs 26.3%; P<0.01), non-HDL-C (-46.8 vs -32.7%; P<0.01), and apo B (-38.9 vs -26.7%; P<0.01). There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo All patients received simvastatin 10 to 40 mg QD			non-HDL-C, apo B after six weeks, 33 weeks and 53 weeks, percentage of patients achieving LDL-C goals	significant difference in HDL-C (P<0.95) or TG (P<0.48) among the treatment groups. After 33 weeks of therapy, ezetimibe was more effective compared to placebo in lowering LDL-C (-54 vs 38.1%; P<0.01), TC (-42.5 vs 29.3%; P<0.01), non-HDL-C (-51.3 vs -35.7%; P<0.01), TG (-20 vs -13.4%; P<0.01) and apo B (-42.6 vs -27.9%; P<0.01). There was no significant difference in HDL-C (P=0.58) among the treatment groups. The percentage of patients achieving the American Academy of Pediatrics acceptable LDL-C goal of <130 mg/dL and ideal LDL-C goal of <110 mg/dL was significantly higher with ezetimibe (77 and 63%, respectively) compared to placebo (53 and 27%, respectively; P<0.01) in patients receiving simvastatin 40 mg/day. After 53 weeks of therapy, the mean percent change in LDL-C in the overall population was -49.1% from baseline. Mean percent changes were -38.5% in TC, -46.4% in non-HDL-C, and median percent changes of -16.6% were observed in TG. The HDL-C levels were 3.3% above baseline levels at trial end.
Masana et al.[35] (2005) Ezetimibe 10 mg QD vs placebo All patients received simvastatin 10 mg/day, titrated up to 80 mg/day.	DB, ES, MC, RCT Patients with primary hypercholesterolemia ≥18 years of age, currently taking a stable daily dose of a statin ≥6 weeks, with LDL-C above the NCEP ATP II guideline target level, TG <350 mg/dL	N=355 48 weeks	Primary: Percent change from baseline in LDL-C between the study groups at week 12 Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, non-HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C at 12 weeks	Primary: At week 12, patients receiving ezetimibe experienced a statistically significant 27% reduction in LDL-C compared to patients receiving placebo (P<0.001). The benefit was maintained up to week 48 of the study. Secondary: At week 12, patients receiving ezetimibe experienced a statistically significant reduction in total cholesterol, TG, non-HDL-C, ratios of LDL-C:HDL-C, and TC:HDL-C, compared to patients receiving placebo (P<0.001). At week 12, patients receiving ezetimibe experienced a non-significant 2.6% increase in HDL-C compared to patients receiving placebo (P=0.07). Treatment-related adverse effects were similar between the two treatments (17 and 19%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no cases of rhabdomyolysis or myopathy during the study.
Gagné et al.[36] (2002) Ezetimibe 10 mg QD vs placebo All patients were receiving statin therapy.	DB, MC, PC, RCT Adults aged ≥18 years, currently on a stable daily dose of a statin for ≥6 weeks, must have been previously instructed on a cholesterol-lowering diet, LDL-C at or above recommended target level for patient's risk category (<160 mg/dL for patients without CHD and ≤1 risk factor, <130 mg/dL for patients without CHD and ≥2 risk factors, ≤100 mg/dL for patients with established but stable CHD or CHD-equivalent disease)	N=769 8 weeks	Primary: Mean percentage change in LDL-C from baseline to end point Secondary: Percentage of patients who achieved NCEP ATP II target levels for LDL-C, HDL-C, TC, TG, adverse events	Primary: There was an additional LDL-C reduction of 25.1% in patients receiving ezetimibe therapy compared to a reduction of 3.7% in patients receiving placebo (P<0.001 for between-group differences). Secondary: Including patients who were technically at LDL-C goal at baseline, 75.5% of patients taking ezetimibe plus statin achieved the prespecified NCEP ATP II target LDL-C levels at end point compared to 27.3% of patients taking placebo plus statin (OR, 19.6; P<0.001). For those patients who were not at target LDL-C levels at baseline, 71.5 vs 18.9% of patients taking ezetimibe and placebo, respectively, achieved target LDL-C goals. HDL-C was increased by 2.7% compared to an increase of 1.0% in patients taking ezetimibe and placebo, respectively (P<0.05). TG decreased by 14.0 and 2.9%, respectively (P<0.001). TC was also improved significantly with coadministration of ezetimibe compared to placebo (P<0.001). The overall incidence of treatment-related adverse events was similar between both groups (21 vs 17%).
Denke et al.[37] (2006) Ezetimibe 10 mg QD vs placebo All patients were	DB, MC, PC, PG, RCT Men and women ≥18 years of age with diabetes, metabolic syndrome without diabetes, or neither disorder who had LDL-C levels exceeding the NCEP ATP III goals who	N=3,030 6 weeks	Primary: LDL-C reduction and additional lipid parameters, safety and tolerability Secondary: Not reported	Primary: After six weeks of treatment, the addition of ezetimibe to ongoing statin therapy reduced LDL-C levels in patients with diabetes by 28%, metabolic syndrome by 24%, or elevated LDL-C levels without diabetes or the metabolic syndrome by 26%, compared to a 3% reduction in the placebo group (P<0.001 for all). TG and HDL-C levels were significantly reduced in patients with diabetes and metabolic syndrome when ezetimibe was added to statin therapy compared to placebo (P<0.002). Non-HDL levels, TC, apo B:apo AI ratio, and CRP levels improved significantly in patients with diabetes and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
receiving statin therapy.	were taking a stable, approved dose of any statin, had been following a cholesterol -lowering diet for ≥6 weeks prior to study entry with TG levels ≤350 mg/dL			patients with elevated LDL-C levels without diabetes or metabolic syndrome when ezetimibe was added to statin therapy compared to placebo. Drug-related adverse events occurred in 5.2% in the placebo group and 5.1% in the ezetimibe group. Drug-related adverse events that led to drug discontinuation occurred in 1.6% in the placebo group and 0.9% in the ezetimibe group. There were no significant differences between the two groups in elevation of ALT, AST or in muscle CK beyond predefined limits. Secondary: Not reported
Pearson et al.[38] (2006) Ezetimibe 10 mg QD vs placebo All patients were receiving statin therapy.	DB, MC, PG, PC, RCT Men and women ≥18 years of age including white, African American, Hispanic or other who followed a cholesterol-lowering diet, were taking a stable approved dose of any US marketed statin for ≥6 weeks before study entry, with LDL-C levels greater than the NCEP ATP III goal	N=3,030 6 weeks	Primary: LDL-C and additional parameters and percentage of patients reaching LDL goal for the NCEP ATP III in racial and ethnic subgroups Secondary: Safety and tolerability	Primary: The addition of ezetimibe to ongoing statin therapy significantly reduced LDL-C, TC, non-HDL and HDL-C levels compared to placebo (P<0.001). This effect was consistent across race and ethnicity (P>0.50 for treatment-by-race interactions). CRP level reduction was statistically significant in patients receiving ezetimibe compared to placebo (P<0.001). The treatment-by-race interaction was not statistically significant (P=0.83), indicating a consistent treatment effect of lowering CRP levels across race and ethnicity groups. Ezetimibe added to statin therapy significantly increased the percentage of patients attaining their LDL-C goal for the NCEP ATP III in African Americans by 63%, Hispanics by 64.8% and whites by 72.3%, compared to placebo (P<0.001). Secondary: The addition of ezetimibe to ongoing statin therapy was well tolerated with an overall safety profile similar in all patient groups by race or ethnicity.
Pearson et al.[39] (2005) EASE	DB, MC, PG, RCT Subanalysis of the	N=3,030 6 weeks	Primary: Mean change from baseline in LDL-C	Primary: Compared to placebo, patients receiving ezetimibe experienced an LDL-C reduction of 23% (white patients), 23% (African American patients), and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD vs placebo All patients were receiving statin therapy.	EASE study; patients >65 years old with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals, on an approved dose of a statin for 6 weeks prior to study entry, following a cholesterol-lowering diet		level, proportion of patients who reached LDL-C target across different races and ethnicities, change in serum cholesterol, TG, HDL at 6 weeks Secondary: Not reported	21% (Hispanic patients) from baseline (P<0.001). The difference in LDL-C lowering among the three races studied was not statistically significant (P>0.5). A significantly greater proportion of patients randomized to ezetimibe achieved their NCEP ATP LDL-C goal compared to placebo (P<0.001). Patients receiving ezetimibe experienced a TC reduction of 15.3 mg/dL from baseline compared to patients receiving placebo (P<0.001). Patients receiving ezetimibe experienced a TG reduction of 11.5 mg/dL from baseline compared patients receiving placebo (P<0.001). Patients receiving ezetimibe experienced an increase in HDL-C of 2.1 mg/dL from baseline compared to patients receiving placebo (P<0.001). Side effects were similar across treatment groups and races. Secondary: Not reported
Mikhailidis et al.[40] (2007) Ezetimibe 10 mg QD vs placebo All patients were receiving statin therapy.	MA (21 trials) Adults ≥18 years with diagnoses of nonfamilial or familial hypercholesterolemia, hyperlipidemia, and homozygous familial sitosterolemia; with LDL-C levels above NCEP ATP II/III guideline criteria	N=5,039 6 to 48 weeks	Primary: Total number of patients attaining LDL-C goal; changes in TC, LDL-C, and HDL-C from baseline to end point Secondary: Not reported	Primary: The analysis of five RCTs indicated that when compared to placebo in combination with a statin, the RR of obtaining the LDL-C treatment goal was higher for patients in the ezetimibe and statin groups (P<0.0001). A WMD between treatments significantly favored the ezetimibe and statin combination therapy over placebo and statin: for TC, a WMD of -16.1% (CI, -17.3 to -14.8); for LDL-C, a WMD of -23.6% (CI, -25.6 to -21.7); and for HDL-C, a WMD of 1.7% (CI, 0.9 to 2.5) (P<0.0001 for all). In an analysis of patients with or without CHD (in addition to hypercholesterolemia), the ezetimibe and statin combination was favored over placebo and statin for the following WMD: LDL-C -23.6% (P<0.0001); TC -16.1% (P<0.0001); HDL-C 1.7% (P<0.0001); TG -10.7%; apo B -17.3%; RR, LDL-C treatment goal 3.4% (P<0.0001). The difference between treatments in all studies favored the ezetimibe and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				statin combination therapy for all outcomes except TG and HDL-C. An analysis of data from a 48-week ES correlated with the pooled estimates of the short-term studies in the MA. This data showed that the ezetimibe and simvastatin combination resulted in significantly lower levels of LDL-C, TC, and TG when compared to the placebo and simvastatin combination (reductions of 20.4, 13.4 and 13.6%, respectively; P<0.001 for the difference between treatments). Secondary: Not reported
Pearson et al.[41] (2009) <u>Group 1</u> Ezetimibe 10 mg QD vs placebo and <u>Group 2</u> Ezetimibe 10 mg QD vs placebo All patients in Group 2 were receiving statin therapy.	MA (11 trials) Patients with hypercholesterolemia and hsCRP ≤10 mg/L	N=5,271 (11 trials) 6 to 12 weeks	Primary: Mean change in hsCRP and LDL-C Secondary: Not reported	Primary: Treatment with ezetimibe monotherapy led to a mean 1% reduction in CRP compared to a mean 5% increase with placebo after 12 weeks (P=0.09). Treatment with ezetimibe and statin combination therapy led to a mean 12% decrease in CRP compared to a mean 1% decrease with statin monotherapy after six to eight weeks (P<0.001). Treatment with ezetimibe monotherapy led to a mean 18% reduction in LDL-C compared to a mean 0.5% increase with placebo after 12 weeks of therapy (P<0.001). Treatment with ezetimibe and statin combination therapy led to a mean 27% decrease in LDL-C compared to a mean 3% decrease with statin monotherapy after six to eight weeks (P<0.001). Secondary: Not reported
Farnier et al.[42] (2005)	DB, MC, PC, RCT	N=619	Primary: Percent change in	Primary: The mean percent change in LDL-C reduction was significantly greater in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg and fenofibrate 160 mg QD vs ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs placebo	Men and women 18 to 75 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or 10-year CHD risk >20%	12 weeks	LDL-C from baseline to study end point Secondary: Percent change in other lipid, non-lipid, and lipoprotein parameters from baseline to study end point	the micronized fenofibrate and ezetimibe group when compared to the other treatment groups (P<0.001 compared to micronized fenofibrate and ezetimibe). These reductions were 13.4% in the ezetimibe group, 5.5% in the micronized fenofibrate group, and 20.4% in the micronized fenofibrate and ezetimibe group. Secondary: When compared to micronized fenofibrate or ezetimibe monotherapy, significant reductions in apo B, non-HDL-C and LDL-C were observed in the micronized fenofibrate and ezetimibe group; P<0.001. When compared to placebo, significant decreases in TG levels and significant increases in HDL-C level were observed in both the micronized fenofibrate plus ezetimibe and micronized fenofibrate treatment groups; P<0.001. The percent changes from baseline to study end point were as follows: -11.8% in TC, 3.9% in HDL-C, -11.1% in TG, and -6.1% in high sensitivity CRP in the ezetimibe group; -10.8% in TC, 18.8% in HDL-C, -43.2% in TG, and -28.0% in hsCRP in the micronized fenofibrate group; -22.4% in TC, 19.0% in HDL-C, -44.0% in TG, and -27.3% in hsCRP in the micronized fenofibrate and ezetimibe group (P<0.05 for all).
Tribble et al.[43] (2008) Ezetimibe 10 mg and fenofibrate 160 mg QD (FENO + EZE) vs ezetimibe 10 mg QD (EZE) vs fenofibrate 160 mg QD (FENO)	DB, MC, PC, RCT Patients 18 to 75 years of age with mixed hyperlipidemia (LDL-C 130 to 220 mg/dL and TG 200 to 500 mg/dL) and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=625 12 weeks	Primary: Changes in cholesterol mass within the major lipoprotein fractions and subfractions and LDL particle distribution profiles and particle size Secondary: Not reported	Primary: The effects of EZE, FENO, and FENO + EZE on VLDL subfractions were similar to those for VLDL overall. All active treatments reduced IDL-C. Treatment with FENO significantly reduced LDL-C1, LDL-C3, and LDL-C4 and significantly increased LDL-C2 compared to placebo. FENO + EZE produced a pattern of changes similar to those of FENO alone. The reductions in LDL-C1 and LDL-C3 were greater with the combination due to the added effects of EZE. There were no significant changes in cholesterol associated with Lp(a). Fenofibrate and FENO + EZE increased median HDL-C2 and HDL-C3 compared to EZE and placebo. In patients treated with EZE, there were reductions in VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL density distributions or

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vs placebo				changes in the HDL-C range. In patients treated with FENO, there were reductions in VLDL-C and IDL-C. HDL-C was increased and there was a shift in the distribution of LDL toward larger, more buoyant LDL particles with a small effect on LDL-C values overall. In patients treated with FENO + EZE, there were reductions in VLDL-C, IDL-C, and LDL-C. HDL-C was increased and there was a shift from smaller, more dense to larger, more buoyant LDL subfractions. EZE did not significantly affect LDL peak particle size. FENO and FENO + EZE increased LDL peak particle size. Secondary: Not reported
McKenney et al.[44] (2006) Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs ezetimibe 10 mg QD for 12 weeks, then fenofibrate 160 mg and ezetimibe 10 mg QD for 48 weeks	DB Patient who completed base study with mixed hyperlipidemia	N=576 48 weeks	Primary: Percent change in LDL-C from baseline of the base study to study end point in the extension Secondary: Percent change from baseline to study end point in TC, HDL-C, TG, non-HDL-C, apo B, apo AI, and hsCRP	Primary: Fenofibrate plus ezetimibe showed significantly greater percent reductions in LDL-C compared to fenofibrate alone (-22.0 vs -8.6; P<0.001). Secondary: Fenofibrate plus ezetimibe showed significantly greater percent reductions from baseline to extension study end point in TC (-23.2 vs -13.6; P<0.001), TG (-46.0 vs -41.0; P=0.002), non-HDL-C (-31.6 vs -19.4; P<0.001), and apo B (-25.2 vs -16.2; P<0.001) compared to fenofibrate. There was a significantly greater percent increase in HDL-C (20.9 vs 17.8; P=0.02) with fenofibrate plus ezetimibe vs fenofibrate alone. There was not a significantly greater percent increase in apo AI (10.1 vs 7.8; P=0.12) with fenofibrate plus ezetimibe vs fenofibrate alone. Reductions in median hsCRP levels were not different between treatments (-25.3 vs -21.1; P=0.46) for fenofibrate plus ezetimibe vs fenofibrate alone, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 12 weeks, then fenofibrate 160 mg for 48 weeks				
Ballantyne et al.[45] (2003) Ezetimibe 10 mg QD and atorvastatin 10 to 80 mg QD vs ezetimibe 10 mg QD vs atorvastatin 10 to 80 mg QD vs placebo	DB, PC, RCT Men and women aged ≥18 years with primary hypercholesterolemia (LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL)	N=628 12 weeks	Primary: Percentage reduction in direct LDL-C from baseline to final assessment Secondary: Change from baseline to final assessment for calculated LDL-C, TC, TG, HDL-C, TC:HDL-C ratio, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, Lp(a), direct LDL-C:HDL-C ratio, adverse events	Primary: There was a significantly greater mean reduction of direct LDL-C from baseline to final assessment in the ezetimibe plus atorvastatin group compared to either atorvastatin alone (P<0.01) or ezetimibe alone (P<0.01). Mean changes in direct LDL-C ranged from -50 to -60% in the combination group compared to -35 to -51% in the atorvastatin alone group (P<0.01). Secondary: Calculated LDL-C was also significantly reduced more commonly in the combination group than all doses of atorvastatin monotherapy (P<0.01). Greater reductions in LDL-C, TC, and TG were observed with increasing doses of atorvastatin monotherapy. However, there was not a favorable dose response with HDL-C. There were similar reductions in LDL-C (50 vs 51%), TC:HDL-C ratio (43 vs 41%), and TG (both 31%) with coadministration of ezetimibe plus atorvastatin 10 mg and the maximal dose of atorvastatin monotherapy, respectively. However, there was a significantly greater increase in HDL-C (9 vs 3%) with the combination group. Reductions in apo B, non–HDL-C, and direct LDL-C:HDL-C ratio from baseline were significantly greater in the combination group compared to both atorvastatin monotherapy (P<0.01 for all) and ezetimibe monotherapy (P<0.01 for all). However, increases in HDL_2-C (P=0.53), HDL_3-C (P=0.06), apo AI (P=0.31), and Lp(a) (P=0.50) did not significantly differ between the combination therapy and atorvastatin monotherapy groups. There also was no significant difference between the combination therapy and ezetimibe

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				monotherapy groups for increases in these same parameters: HDL_2-C (P=0.08), HDL_3-C (P=0.67), apo AI (P=0.80), and Lp(a) (P=0.92). The combination of ezetimibe plus atorvastatin was well-tolerated. Treatment-emergent adverse events were reported in 17% of patients receiving atorvastatin monotherapy and 23% of patients receiving combination therapy. The majority of adverse events were mild to moderate in severity.
Kerzner et al.[46] (2003) Ezetimibe 10 mg QD and lovastatin 10 to 40 mg QD vs ezetimibe 10 mg QD vs lovastatin 10 to 40 mg QD vs placebo	DB, MC, PC, RCT Men and women aged ≥18 years with mean plasma LDL-C 145 to 250 mg/dL as calculated by Friedewald equation, mean TG ≤350 mg/dL	N=548 12 weeks	Primary: Percentage decrease in directly measured LDL-C from baseline to study end point Secondary: Change from baseline to end point for calculated LDL-C, TC, TG, HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, apo AI, direct LDL-C:HDL-C ratio, adverse events	Primary: The reduction in plasma levels of direct LDL-C from baseline to end point was significantly greater in the combination group of ezetimibe plus lovastatin compared to either lovastatin or ezetimibe monotherapy (P<0.01 for both). The mean percentage decrease in direct LDL-C in the combination group was significantly greater than the decrease obtained from the corresponding lovastatin dose or next higher dose of lovastatin monotherapy (P<0.01). The mean percentage change in LDL-C achieved with combination ezetimibe plus lovastatin 10 mg was similar to the highest lovastatin dose of 40 mg monotherapy (P=0.10). Secondary: In comparison to lovastatin monotherapy, the combination group significantly improved calculated LDL-C, TC, TG, HDL-C, apo B, non–HDL-C, HDL_2-C, HDL_3-C, direct LDL-C:HDL-C ratio (P<0.01 for all), and apo AI (P=0.04). The combination of ezetimibe plus lovastatin significantly increased HDL-C at lovastatin doses of 20 and 40 mg compared to the same lovastatin monotherapy dose (P<0.01 and P<0.02, respectively) and significantly decreased TG levels (P<0.01 for both). Treatment-related adverse events were reported for 16% of patients receiving lovastatin monotherapy and 17% of patients receiving combination therapy. The safety profile for the combination group was similar to that for the lovastatin monotherapy and placebo group.
Melani et al.[47]	DB, MC, PC, RCT	N=538	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2003) Ezetimibe 10 mg QD and pravastatin 10 to 40 mg QD vs ezetimibe 10 mg QD vs pravastatin 10 to 40 mg QD vs placebo	Men and women 20 to 86 years old with primary hypercholesterolemia (LDL-C 150 to 250 mg/dL and TG ≤350 mg/dL)	12 weeks	Percent change in direct LDL-C from baseline to study end point Secondary: Mean change and percent change from baseline in LDL-C as calculated by the Friedewald equation, TC, TG, HDL-C, direct LDL-C:HDL-C and TC:HDL-C ratio, non–HDL-C, apo AI, apo B, HDL_2-C, HDL_3-C, Lp(a)	A mean percent change of –38% for the combination therapy and -24% for pravastatin monotherapy was observed. The combination therapy was significantly more effective at reducing plasma levels of direct LDL-C from baseline to end point (P<0.01). The combination group had a mean percentage change in direct LDL-C ranging from -34 to -41% compared to -20 to –29% for individual doses of pravastatin monotherapy. When the combination therapy was compared to its corresponding pravastatin dose, the incremental mean percentage reductions in direct LDL-C were statistically significant in favor of the combination therapy (P≤0.01). In addition, the coadministration of ezetimibe plus pravastatin 10 mg produced a larger mean percentage reduction in direct LDL-C compared to the highest dose of pravastatin monotherapy (P≤0.05). Secondary: In comparison to pravastatin monotherapy, the combination therapy improved calculated LDL-C, TG, TC, apo B, non–HDL-C, direct LDL-C:HDL-C, and TC:HDL-C (P<0.01 for all). Both direct and calculated LDL-C levels at all pravastatin doses were significantly reduced in the combination group (P<0.01). TG was also significantly reduced in the combination group at pravastatin doses of 10 and 20 mg compared to pravastatin monotherapy (P<0.05). Although the combination therapy produced greater increases in HDL-C at the 10 and 40 mg doses, it was not significant. The differences in change in HDL_2-C, HDL_3-C, apo AI, and Lp(a) between the combination group and pravastatin monotherapy were determined to be not significant (P value not significant). Coadministration of ezetimibe and pravastatin was well tolerated and the overall safety profile was similar to pravastatin monotherapy and placebo. There was no evidence to suggest that combination therapy would increase the risk of developing any non-laboratory adverse event.
Ose et al.[48] (2007) Simvastatin 10, 20,	DB, ES, MC, RCT Patients 22 to 83 years, with primary hyper-	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level, TG, TC,	Primary: Across all doses, patients receiving ezetimibe-simvastatin experienced a statistically significant LDL-C reduction from baseline compared to the simvastatin monotherapy group (53.7 vs 38.8%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40, or 80 mg/day vs ezetimibe-simvastatin 10-10, 10-20, 10-40, and 10-80 mg/day vs ezetimibe 10 mg QD vs placebo	cholesterolemia (LDL-C between 145 and 250 mg/dL and TG <350 mg/dL) who were randomized to ezetimibe-simvastatin 10-10, 10-20, 10-40, or 10-80 mg combination tablet, simvastatin 10, 20, 40, or 80 mg monotherapy, ezetimibe 10 mg, or placebo		non-HDL, CRP, LDL-C:HDL-C ratio, TC:HDL-C ratio, proportion of patients reaching LDL-C target (<100 or <70 mg/dL) Secondary: Not reported	Across all doses, patients receiving ezetimibe-simvastatin combination therapy experienced a statistically significant reduction from baseline in TG, TC, non-HDL, CRP, LDL-C:HDL-C ratio, and TC:HDL-C ratio compared to the simvastatin monotherapy group (P<0.001). Significantly greater proportion of patients randomized to the ezetimibe-simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (79.2 vs 47.9%; P<0.001). A greater proportion of patients randomized to the ezetimibe-simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (30.4 vs 7%; P<0.001). The incidence of drug-related adverse effects was similar in the ezetimibe-simvastatin and simvastatin monotherapy groups (7.4 vs 5.5%, respectively). Secondary: Not reported
Goldberg et al.[49] (2004) Ezetimibe 10 mg/day and simvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day	DB, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, ALT and AST ≤2 times the upper limit of normal, no active liver disease, CK ≤1.5 times the upper limit of normal	N=887 20 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP; proportion of patients reaching their NCEP ATP	Primary: Averaged across all doses, combination therapy was associated with a significant 14.8% reduction in LDL-C at 12 weeks compared to simvastatin (53.2 vs 38.5%; P<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (P<0.001). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			III LDL-C goal <130 or <100 mg/dL at 12 weeks	Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130 or <100 mg/dL at 12 weeks compared to simvastatin (92 and 82% vs 82 and 43%, respectively; P<0.001). Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (P=0.53). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups, but were more frequent than with ezetimibe and placebo (13, 14, 9 and 9%, respectively; P values not reported).
Davidson et al.[50] (2002) Ezetimibe 10 mg/day plus simvastatin 10, 20, 40, or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients >18 years of age with primary hypercholesterolemia	N=668 20 week	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (49.9 vs 36.1%; P<0.001). Similar results were observed with combination therapy compared to ezetimibe (49.9 vs 18.1%; P<0.001). Combination therapy (simvastatin 10 mg) and simvastatin 80 mg produced a 44% reduction in LDL-C at 12 weeks (P value not reported). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks, compared to the next highest dose of simvastatin (P<0.01). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C and apo B at 12 weeks compared to simvastatin (P<0.01 for all). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to simvastatin (P=0.03). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non–HDL-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				C and apo B at 12 weeks compared to ezetimibe (P<0.01 for all). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to ezetimibe (P=0.02). A significantly greater proportion of patients receiving combination therapy experienced a reduction in LDL-C >50% from baseline compared to simvastatin (P value not reported). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups (72 vs 69%, respectively; P value not reported).
Bays et al.[51] (2004) Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients 18 to 80 years of age with primary hypercholesterolemia with LDL-C >145 but ≤150 mg/dL and TG ≤350 mg/dL	N=1,528 24 weeks	Primary: Percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP; proportion of patients reaching their NCEP ATP III LDL-C goal of <130, <100 or <70 mg/dL at 12 weeks	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (53 vs 39%; P<0.001) and ezetimibe (53 vs 18.9%; P<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (P<0.001). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130, <100 or <70 mg/dL at 12 weeks compared to simvastatin (92.2, 78.6 and 38.7 vs 79.2, 45.9 and 7.0%, respectively; P<0.001 for al). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (P=0.607).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Treatment-related adverse effects were similar in the pooled simvastatin, combination and ezetimibe groups, but were more frequent than placebo (14.8, 15.1, 12.8 and 8.1%, respectively; P values not reported).
Feldman et al.[52] (2006) Ezetimibe-simvastatin 10-10, 10-20, 10-40, or 10-80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	MA (3 DB, PC, RCTs) Patients with primary hypercholesterolemia	N=3,083 28 weeks	Primary: Percent change from baseline in LDL-C, TG, non-HDL-C, apo B and hsCRP; achievement of LDL-C <100 mg/dL at week-12 among patients <65 and ≥65 years of age Secondary: Not reported	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C, TG, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (*P*<0.001 for all). These affects did not differ between the older and younger patients (*P* value not reported). Combination therapy and simvastatin produced comparable increases in HDL-C (8 vs 7%, respectively; *P* value not reported). Significantly more patients, in all age groups, receiving combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 12 compared to patients receiving simvastatin (79 vs 42%; *P*<0.001). Similar results were observed with a LDL-C goal <70 mg/dL (37 vs 6%; *P*<0.001). Treatment-related adverse effects were similar with simvastatin and combination therapy, regardless of dose used and age group (*P* values not reported). Secondary: Not reported
Pearson et al.[53] (2007) Atorvastatin 10, 20, 40, or 80 mg/day for 6 weeks vs simvastatin 10, 20, 40, or 80 mg/day for 12 weeks	MA (4 trials) Three identical, prospective 12-week studies randomizing patients to placebo, ezetimibe, ezetimibe with simvastatin or simvastatin alone, and one phase III double-blind, active-controlled study allocating patients to	N=4,373 up to 12 weeks	Primary: Change from baseline in LDL-C level, CRP, proportion of patients reaching LDL-C target (<100 mg/dL or <70 mg/dL) Secondary: Not reported	Primary: Across all doses, patients receiving ezetimibe plus simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the simvastatin monotherapy group (52.5 vs 38%; P<0.001). Across all doses, patients receiving ezetimibe plus simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the atorvastatin monotherapy group (53.4 vs 45.3%; P<0.001). Across all doses, patients on the ezetimibe plus simvastatin combination therapy experienced a statistically significant CRP reduction from baseline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ezetimibe 10 mg/day for 12 weeks vs ezetimibe 10 mg/day added to simvastatin 10, 20, 40, or 80 mg/day for up to 12 weeks vs placebo for 12 weeks	ezetimibe/simvastatin or atorvastatin for 6 weeks			compared to the simvastatin monotherapy group (31 vs 14.3%; P<0.001). Patients on the ezetimibe plus simvastatin combination therapy experienced a similar CRP reduction from baseline compared to the atorvastatin monotherapy group (25.1 vs 24.8%). The reduction in CRP from baseline was not significantly different between simvastatin 10 mg and placebo groups (P>0.10). Significantly greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the simvastatin group (78.9 vs 43.1%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin group (37 vs 5.7%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <100 mg/dL, compared to the atorvastatin group (79.8 vs 61.9%; P<0.001). Significantly greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the atorvastatin group (36.2 vs 16.8%; P<0.001). Secondary: Not reported
Ansquer et al.[54] (2009) Ezetimibe 10 mg QD and fenofibrate (Tricor®) 145 mg QD vs	DB, MC, RCT Patients 18 to 70 years of age with type IIb dyslipidemia (LDL-C ≥160 mg/dL, TG 150-405 mg/dL) and ≥2 features of the metabolic syndrome according to the NCEP	N=60 12 weeks	Primary: Percentage change from baseline in TG and HDL-C Secondary: Percentage change in LDL-C, non-HDL-C, remnant-like particle	Primary: Fenofibrate plus ezetimibe and fenofibrate reduced TG by -38.3% (P value not significant) and increased HDL-C to a similar extent (11.5 and 7.9%, respectively; P=0.282). Secondary: Fenofibrate plus ezetimibe reduced LDL-C by -36.2% compared to -22.4% with fenofibrate and -22.8% with ezetimibe (P<0.001 for both). Fenofibrate plus ezetimibe lowered non-HDL-C by -36.2% compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ezetimibe 10 mg QD vs fenofibrate (Tricor®) 145 mg QD	ATP III definition		cholesterol (RLP-C) and related parameters, change in glucose metabolism parameters, hsCRP, safety	fenofibrate (-24.8%) and ezetimibe (-20.9%) (P value not reported). There was no significant difference between fenofibrate plus ezetimibe and fenofibrate with regards to RLP-C (-36.2 vs -30.7%; P value not significant). Ezetimibe was less effective than fenofibrate plus ezetimibe (-17.3%; P<0.001). The effect of fenofibrate plus ezetimibe on LDL particle size (+2.1%) was similar to that of fenofibrate (+1.9%). Fenofibrate plus ezetimibe was more effective than monotherapy with fenofibrate or ezetimibe in reducing apo B (-33.3%). Fenofibrate plus ezetimibe had the same effect as fenofibrate on apo AI (+7.9 vs +5.1%, respectively) and apo AII (+24.2 vs +21.2%, respectively; P value not reported). Fenofibrate plus ezetimibe and fenofibrate reduced hsCRP to a similar degree. There was a higher incidence of treatment-related adverse events with fenofibrate/ezetimibe, which was primarily due to abnormal laboratory changes, including moderate increases in CK, liver enzymes, and blood creatinine.
Coll et al.[55] (2006) Ezetimibe 10 mg QD vs fluvastatin XR 80 mg QD	RCT HIV patients, ≥6 months on stable HAART, ≥18 years of age, fasting LDL-C ≥3.30 mmol/L	N=20 6 weeks	Primary: LDL-C, TC, endothelial function Secondary: Not reported	Primary: Ezetimibe-treated patients experienced a 20% (P=0.002) LDL-C reduction and a 10% TC reduction (P=0.003). Fluvastatin-treated patients experienced a 24% LDL-C reduction (P=0.02) and a 17% TC reduction (P=0.06). There were no significant differences in lipid-lowering ability between groups. Ezetimibe-treated patients did not experience significant changes in endothelial function. Fluvastatin-treated patients experienced an increase in the rate of endothelial function by 11% (P=0.5). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Stein et al.[56] (2004) Ezetimibe 10 mg QD and atorvastatin 10 mg QD (titrated up to 40 mg/day) vs atorvastatin 20 mg QD (titrated up to 80 mg/day)	DB, DD, MC Patients ≥18 years of age with primary hypercholesterolemia and documented CHD, ≥2 cardiovascular risk factors, or heFH with an LDL-C level ≥130 mg/dL despite treatment with atorvastatin 10 mg	N=621 14 weeks	Primary: Percentage of patients achieving an LDL-C level ≤100 mg/dL after 14 weeks randomization Secondary: Effects on other lipid parameters four weeks after randomization	Primary: When compared to atorvastatin monotherapy, a significantly higher percentage of patients in the ezetimibe and atorvastatin reached an LDL-C level ≤100 mg/dL after 14 weeks randomization, respectively (7 vs 22%; P<0.01). Secondary: When compared to atorvastatin monotherapy, significant reductions in LDL-C, TC and TG levels were observed in patients in the ezetimibe and atorvastatin (P<0.01). Respectively, percent changes between combination vs atorvastatin monotherapy were -22.8 vs -8.6% (mean change) in LDL-C levels, -17.3 vs -6.1% in TC levels (mean change), and -9.3 vs -3.9% (median change) in TG levels (P<0.01 for all). Nonsignificant changes were observed in HDL-C levels.
Piorkowski et al.[57] (2007) Ezetimibe 10 mg QD and atorvastatin 10 mg QD vs atorvastatin 40 mg QD	RCT Patients 18 to 80 years of age with clinically stable angiographically documented CHD and LDL-C >2.5 mmol/L despite ongoing atorvastatin 10 to 20 mg/day, receiving aspirin and clopidogrel	N=56 4 weeks	Primary: Change in liver transaminases, CK, HDL-C, LDL-C, and TG from baseline, percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL-C in either group. Both groups exhibited a statistically significant reduction in LDL-C from baseline (P<0.005). There was no statistically significant difference between the two groups in degree of LDL-C reduction from baseline. Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in TG level from baseline (P<0.005 and P<0.05, respectively). There was no statistically significant difference between the two groups in the percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L). Secondary: Not reported
Zieve et al.[58] (2010)	DB, MC, PG, RCT	N=1.053	Primary: Percent change in	Primary: After six weeks of therapy, treatment with ezetimibe plus atorvastatin led

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ZETELD Ezetimibe 10 mg QD for 12 weeks and atorvastatin 10 mg QD for 6 weeks, followed by atorvastatin 20 mg QD for 6 weeks vs atorvastatin 20 mg QD for 6 weeks, followed by atorvastatin 40 mg for 6 weeks	Patients ≥65 years of age at high risk for CHD with or without AVD who had not reached a LDL-C <70 mg/dL or <100 mg/dL, respectively, after receiving atorvastatin 10 mg/day	12 weeks	LDL-C aftersix6 weeks Secondary: Percentage of patients achieving LDL-C <70 mg/dL and <100 mg/dL for high-risk patients without AVD and <70 mg/dL for high-risk patients with AVD, HDL-C, non-HDL-C, TG, TG, apo B, apo AI, TC:HDL-C, apo B:apo AI, LDL-C:HDL-C, non-HDL-C:HDL-C	to a significantly greater reduction in LDL-C compared to atorvastatin monotherapy (-29 vs -15%; P<0.001). Secondary: The percentage of patients achieving LDL-C <70 mg/dL and LDL-C <100 mg/dL (without AVD) or <70 mg/dL (with AVD) was significantly greater with ezetimibe plus atorvastatin compared to atorvastatin monotherapy at week six and week 12 (P<0.001). After six weeks of therapy, treatment with ezetimibe plus atorvastatin led to significantly greater changes in HDL-C (+3 vs +1%; P=0.02), TC (-16 vs -8%; P<0.001), non-HDL-C (-24 vs -11%; P<0.001), TG (-13 vs -6%; P<0.001), apo B (-17 vs -8%; P<0.001), TC:HDL-C (-17 vs -8%; P<0.001), LDL-C:HDL-C (-27 vs -13%; P<0.001), apo B:apo AI (-15 vs -5%; P<0.001), and non- HDL-C:HDL-C (-24 vs -11%; P<0.001). At week 12, significantly greater changes in favor of ezetimibe plus atorvastatin occurred in HDL-C, TC, non-HDL-C, apo B, apo AI, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C. There was no significant difference among the treatment groups in apo AI at week six, high-sensitivity C-reactive protein at weeks six and 12, and TG at week 12.
Conard et al.[59] (2008) Ezetimibe 10 mg QD and atorvastatin 20 mg QD vs atorvastatin 40 mg QD	DB, MC, PG, RCT Patients 18 to 79 years of age at moderately high risk for CHD who were receiving atorvastatin 20 mg QD with LDL-C levels of 100 mg/dL to 160 mg/dL and TG ≤350 mg/dL	N=196 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <100 mg/dL, percent change TG, TC, HDL-C, non-HDL-C, apo AI, apo B, TC: HDL-C, LDL-C:HDL-C, apo	Primary: Treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-31 vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe plus atorvastatin achieved the NCEP ATP III LDL-C goal <100 mg/dL compared to atorvastatin 40 mg (84 vs 49%, P<0.001). Treatment with ezetimibe plus atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C than treatment with atorvastatin 40 mg (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			B:apo AI, non-HDL-C:HDL-C, hsCRP	There was no significant difference in HDL-C, TG, apo AI, and hsCRP among the treatment groups.
Leiter et al.[60] (2008) Ezetimibe 10 mg QD and atorvastatin 40 mg QD vs atorvastatin 80 mg QD	DB, MC, PG, RCT Patients 18 to 79 years of age at high risk for CHD (CHD or those with a CHD risk equivalent medical condition) who were receiving atorvastatin 40 mg QD with LDL-C levels of 70 mg/dL to 160 mg/dL and TG ≤350 mg/dL	N=579 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <70 mg/dL, percent change TG, TC, HDL-C, non-HDL-C, apo AI, apo B, TC: HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C, hsCRP	Primary: Treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-27 vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe plus atorvastatin achieved the NCEP ATP III LDL-C goal <70 mg/dL compared to atorvastatin 80 mg (74 vs 32%, respectively; P<0.001). Treatment with ezetimibe plus atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C compared to atorvastatin 80 mg (P<0.001). There was no significant difference in HDL-C, TG, apo AI, and hsCRP among the treatment groups.
Conrad et al.[61] (2010) Atorvastatin 40 mg/day plus ezetimibe 10 mg/day vs atorvastatin 80 mg/day	DB, MC, PG, RCT Patients 18 to 80 years of age at NCEP ATP III high risk with CHD or CHD risk equivalent, LDL-C ≥70 and ≤160 mg/dL and taking a stable dose of a statin of equal or lesser potency than atorvastatin 40 mg/day or were taking atorvastatin 40 mg/day with good adherence or were stain, ezetimibe or	N=568 6 weeks	Primary: Proportion of patients reaching LDL-C <70 mg/dL; percent changes from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG, apo B, apo AI, TC:HDL-C, LDL-C/HDL-C, apo B/AI, non-HDL-C/HDL-C and hsCRP Secondary: Adverse events	Primary: The proportion of patients reaching LDL-C <70 mg/dL was greater with combination therapy, with a larger between-treatment difference in proportions in patients with metabolic syndrome (without type 2 diabetes) compared to patients with type 2 diabetes or neither condition, which had similar between-treatment differences in proportions. In patients with type 2 diabetes, metabolic syndrome and those with neither condition, the reduction in LDL-C was greater in patients treated with combination therapy compared to doubling the dose of atorvastatin. The mean between-treatment difference (95% CI) was -17.4 (-21.7 to -13.1), -16.0 (-22.3 to -9.6) and -14.3% (-20.9 to -7.8). Reductions in TC, non-HDL-C and apo B were greater with combination therapy in all three patient populations. The magnitude of the differences between treatments in TG was numerically greater in patients with type 2 diabetes compared to the other two patient populations, but overall the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	ezetimibe/simvastatin naïve			differences were relatively small. There were no appreciable changes or between-treatment differences in HDL-C and apo AI in any patient population. The percent reduction in lipid ratios was greater with combination therapy in all three patient populations and between-treatment differences were consistent. Combination therapy resulted in numerically greater reductions from baseline in hsCRP in all three patient populations. The between-treatment differences in patients with metabolic syndrome (-11.8) and type 2 diabetes (-10.3) were larger than in patients with neither condition (-3.2). Secondary: There were comparable proportions of patients with one or more adverse event in the type 2 diabetes and metabolic syndrome populations regardless of treatment. The most commonly reported adverse events were gastrointestinal related.
Uemura et al.[62] (2012) Ezetimibe 10 mg/day plus atorvastatin 10 mg/day vs atorvastatin 20 mg	AC, DB, OL, PRO, XO Patients with impaired glucose tolerance or type 2 diabetes who were receiving atorvastatin (10 mg/day) for dyslipidemia, and had CAD with angiographic stenosis (≥50% diameter stenosis on quantitative coronary angiography) or a history of coronary revascularization for stable angina	N=39 24 weeks	Primary: Change from baseline in MDA-LDL, HDL, triglycerides, apo AI, apo B, and RLP Secondary: Not reported	Primary: Ezetimibe plus atorvastatin significantly reduced the serum concentration of MDA-LDL from 109.0±31.9 IU/L at baseline to 87.7±29.4 IU/L after 12 weeks (P=0.0009). The MDA-LDL was not significantly decreased in patients receiving atorvastatin monotherapy (from 109.0±31.9 IU/L to 106.0±34.9 IU/L (P value not significant)). The MDA-LDL level was significantly lower after treatment with ezetimibe plus atorvastatin compared to monotherapy with a higher dose of atorvastatin (P=0.0006). Both treatments significantly improved HDL from baseline (P<0.05 for both); however, there was no difference between the treatment groups (P>0.05). There were no statistically significant differences between combination therapy and atorvastatin monotherapy with regard to a reduction in serum triglycerides (P>0.05). Both treatment regimens significantly reduced total cholesterol from baseline (P<0.05 for both comparisons); however, combination therapy reduced total cholesterol significantly further than atorvastatin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				monotherapy (147.8±21.3 vs 164.3±25.8 mg/dL; P<0.05). Combination treatment with ezetimibe and atorvastatin increased apo AI compared to baseline (P<0.05). Both treatment groups reduced apo B compared to their respective baseline values (P<0.05 for both). Combination therapy was associated with a statistically significant reduction in apo B compared to atorvastatin monotherapy (73.9±18.0 mg/dL vs 83.7±17.2 mg/dL, respectively; P<0.05). A significantly lower apo B/apo AI ratio was achieved with combination therapy compared to atorvastatin monotherapy (P<0.05). No statistically significant difference occurred between combination therapy and atorvastatin monotherapy with regard to RLP-cholesterol (P>0.05).
Constance et al.[63] (2007) Atorvastatin 20 mg QD for 6 weeks, following a 4 week atorvastatin 10 mg QD run-in period vs ezetimibe 10 mg QD added to simvastatin 20 mg QD for 6 weeks, following a 4 week atorvastatin 10 mg QD run-in period vs ezetimibe 10 mg	DB, MC, PG, RCT Patients ≥18 years of age, with type 2 diabetes, HbA_{1c} ≤10%, ALT/AST levels <1.5 times the upper limit of normal, CK <1.5 times the upper limit of normal	N=661 6 weeks	Primary: Change from baseline in LDL-C at six weeks Secondary: Change from baseline in TC, HDL-C, TG, non-HDL-C, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio	Primary: Across all doses, patients on the ezetimibe plus simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline compared to the atorvastatin 20 mg monotherapy group (P≤0.001). Secondary: Across all doses, patients on the ezetimibe plus simvastatin combination therapy experienced a statistically significant reduction from baseline in TC, non-HDL, apo B, LDL-C:HDL-C ratio, and TC:HDL-C ratio compared to the atorvastatin 20 mg monotherapy group (P≤0.001). Patients on the ezetimibe 10 mg plus simvastatin 40 mg combination therapy experienced a statistically significant reduction in CRP from baseline compared to the atorvastatin 20 mg monotherapy group (P=0.006). Significantly greater proportion of patients randomized to the ezetimibe 10 mg plus simvastatin 20 mg and ezetimibe 10 mg and simvastatin 40 mg combination therapy achieved LDL-C <2.5 mmol/L, compared to the atorvastatin 20 mg group (90.5, 87, and 70.4%, respectively; P≤0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD added to simvastatin 40 mg QD for 6 weeks, following a 4 week atorvastatin 10 mg QD run-in period				The incidence of drug-related adverse effects was similar in the ezetimibe/simvastatin 10/20 mg and 10/40 mg combination therapy and atorvastatin monotherapy groups (0.5, 0.5, and 2.3%, respectively).
Hing Ling et al.[64] (2012) Atorvastatin 40 mg/day vs ezetimibe 10 mg/day plus simvastatin 40 mg/day All patients received atorvastatin 20 mg/day for six weeks at baseline.	AC, DB, MC, RCT Patients 18 to 79 years of age at high risk for CHD with primary hypercholesterolemia, LDL >100 mg/dL and <160 mg/dL, triglycerides <350 mg/dL, liver function tests within normal limits without active liver disease	N=250 6 weeks	Primary: Change from baseline in LDL-C, Secondary: TC, HDL, CRP, Apo AI, Apo B, TG, non-HDL, LDL-C/HDL ratio, TC/HDL ratio, non-HDL/HDL ratio, Apo AI/Apo B ratio	Primary: After six weeks, treatment with ezetimibe/simvastatin resulted in significantly greater reductions from baseline in LDL-C levels compared to treatment with atorvastatin 40 mg (-26.8 vs -11.8%; P<0.001). Secondary: Treatment with ezetimibe/simvastatin resulted in significantly greater reductions in TC (P<0.001), non-HDL-C (P<0.001), Apo B (P=0.002), Apo AI (P<0.001), and all lipid ratios (P<0.001 for all). There were no significant differences between treatments with regard to the change from baseline in TG (P=0.593), HDL-C (P=0.211), or CRP (P=0.785).
Goldberg et al.[65] (2006) VYTAL Atorvastatin 10, 20, or 40 mg/day vs simvastatin 20 or 40 mg/day and ezetimibe 10	DB, MC, PG, RCT Adult patients with type 2 diabetes between 18 and 80 years of age with HbA_{1c} ≤8.5%, LDL-C >100 mg/dL and a TG level <400 mg/dL	N=1,229 6 weeks	Primary: Percent reduction in LDL-C level at week six Secondary: Proportion of patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of	Primary: Patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week six of the study compared to patients receiving atorvastatin 10 or 20 mg (53.6, 38.3, and 44.6%, respectively; P<0.001). Patients randomized to simvastatin 40 mg plus ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week six of the study compared to patients receiving atorvastatin 40 mg (57.6 and 50.9%, respectively; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day			patients who achieved LDL-C level of <100 mg/dL, percent change from baseline in HDL-C, non-HDL-C, TC, TG, and CRP	A greater proportion of patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy achieved LDL-C <70 mg/dL compared to patients receiving atorvastatin 10 or 20 mg (59.7, 21.5, and 35%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 40 mg plus ezetimibe 10 mg therapy achieved LDL-C <70 mg/dL compared to patients receiving atorvastatin 40 mg (74.4 and 55.2%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 20 mg plus ezetimibe 10 mg therapy achieved LDL-C <100 mg/dL compared to patients receiving atorvastatin 10 or 20 mg (90.3, 70, and 82.1%, respectively; P=0.007). A greater proportion of patients randomized to simvastatin 40 mg plus ezetimibe 10 mg therapy achieved LDL-C <100 mg/dL compared to patients receiving atorvastatin 40 mg (93.4 and 88.8%, respectively; P=0.07). Patients randomized to simvastatin plus ezetimibe combination therapy, at all doses, experienced a significant increase in HDL-C level (P≤0.001), a greater reduction in TC, and non-HDL-C (P<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy experienced a significant reduction in CRP and TG level compared to patients receiving atorvastatin (P=0.02). Side effects were similar in the simvastatin plus ezetimibe and atorvastatin groups (19.85 vs 22.7%).
Kumar et al.[66] (2009) Ezetimibe 10 mg/day plus fenofibrate 160	RCT, XO Patients with hypercholesterolemia requiring pharmacotherapy	N=43 12 weeks	Primary: Percentage reduction of LDL-C Secondary:	Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (P=0.46). Secondary: Both treatments provided similar improvements in TC (-25.1 vs -24.6%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs atorvastatin 10 mg/day			Percent changes from baseline in TC, HDL-C and TG	P=0.806) and HDL-C (10.1 vs 8.9%; P=0.778). Combination therapy showed a trend towards a greater reduction in TGs (25.4 vs 14.5%; P=0.079), although there were no significant difference between the two treatments in terms of the improvement in TC:HDL-C (-29.0 vs -28.7%; P=0.904).
Stojakovic et al.[67] (2010) Ezetimibe 10 mg/day plus fluvastatin 80 mg/day vs fluvastatin 80 mg/day	PRO, RCT, SB Patients with CHD or CHD risk equivalent with LDL-C 100 to 160 mg/dL	N=90 12 weeks	Primary: Changes from baseline in lipids, apolipoproteins and lipoprotein subfractions Secondary: Not reported	Primary: After 12 weeks, TC, LDL-C and apo B were significantly lowered with both treatments, but the reductions were significantly greater with combination therapy (P<0.001 for all). Combination therapy significantly reduced TG, apo CII, apo CIII and apo E compared to baseline (P<0.001 for all) and fluvastatin (P=0.008, P=0.002 and P=0.007). Apo AI and AII increased with fluvastatin and decreased with combination therapy. Accordingly, HDL-C increased with fluvastatin and decreased with combination therapy, but the difference was not significant (P=0.080). Similar results were observed when only patients with type 2 diabetes were analyzed. Secondary: Not reported
Stein et al.[68] (2008) Fluvastatin XL 80 mg QD vs ezetimibe 10 mg QD vs fluvastatin XL 80 mg QD and ezetimibe 10 mg	DB, MC, PG, RCT Patients ≥18 years of age with dyslipidemia who had previously documented muscle related side effects that had led to cessation of statin treatment or patients currently receiving statin treatment whose quality of life was affected by muscle related side effects and required	N=218 12 weeks	Primary: Percent decrease in LDL-C Secondary: LDL:HDL-C, TC, TG, apo B, proportion of patients achieving LDL-C goal	Primary: LDL-C was reduced by 15.6, 32.8, and 46.1% with ezetimibe monotherapy, fluvastatin XL monotherapy, and fluvastatin XL plus ezetimibe combination therapy, respectively (fluvastatin XL vs ezetimibe: -17.1%, P<0.0001; fluvastatin XL plus ezetimibe vs ezetimibe: -30.4%, P<0.0001). Secondary: Treatment with fluvastatin XL monotherapy and fluvastatin XL plus ezetimibe combination therapy led to a greater reduction in LDL:HDL-C, TC, TG, and apo B levels compared to ezetimibe monotherapy (all, P<0.0001). More patients achieved their target LDL-C goal with fluvastatin XL monotherapy and fluvastatin XL plus ezetimibe combination therapy compared to ezetimibe monotherapy (P<0.001 for fluvastatin XL

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QD	switching to an alternative treatment			monotherapy or combination therapy vs ezetimibe monotherapy). There were no serious adverse events, rhabdomyolysis, or creatine kinase increases ≥10 times upper limit of normal. Muscle related side effects were reported in 24% of patients receiving ezetimibe monotherapy compared to 17% of patients in the fluvastatin XL group and 14% of patients in the fluvastatin XL plus ezetimibe combination group. Differences in recurrence of muscle related side effects were not statistically different between treatment groups.
Alvarez-Sala et al.[69] (2008) Fluvastatin XL 80 mg QD (nighttime) and ezetimibe 10 mg QD vs fluvastatin XL 80 mg QD (nighttime)	MC, OL, PG, RCT Patients 18 to 75 years of age with primary hypercholesterolemia (LDL-C ≥130 mg/dL and TG ≤400 mg/dL)	N=89 12 weeks	Primary: Percentage change in LDL-C Secondary: Percentage change in HDL-C and TG, proportions of patients achieving NCEP ATP III LDL-C goals, change in hsCRP and other markers of inflammation, and safety	Primary: Fluvastatin XL plus ezetimibe lowered mean LDL-C from 197 mg/dL to 97 mg/dL (-49.9%) and fluvastatin XL alone lowered mean LDL-C from 216 to 135 mg/dL (-35.2%) after 12 weeks of therapy (P<0.001). Secondary: Fluvastatin XL plus ezetimibe combination was associated with a significantly greater reduction from baseline in TC, TG, and apo B than fluvastatin XL alone (P<0.05 for all). There was no significant change in HDL-C level with either treatment regimen. A greater proportion of patients receiving the fluvastatin XL plus ezetimibe achieved NCEP ATP III LDL-C goals at week 12 compared to those receiving fluvastatin XL alone (86.5 vs 66.7%; P=0.042). There were no significant changes in levels of hsCRP with either treatment regimen. In patients with higher baseline hsCRP levels, the coadministration of fluvastatin XL with ezetimibe was associated with a reduced level of this inflammatory marker. Treatment with fluvastatin XL plus ezetimibe or fluvastatin XL alone was associated with significant reductions in IL-1β (21%; P<0.001 and 13%; P<0.002, respectively). No significant changes were seen in levels of interleukin-6, tumor necrosis factor-α, soluble P-selectin, or soluble vascular cell adhesion molecule-1. There was no significant difference in the incidence of adverse events between the treatment groups. Most adverse events were mild or moderate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in intensity, with headache being the most common (8.5%).
Winkler et al.[70] (2009) Fluvastatin 80 mg/day plus fenofibrate 200 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 mg/day	MC, OL, RCT, XO Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist circumference ≥94 (men) or ≥80 cm (females) plus 1 of the following: TG ≥150 mg/dL, BP (≥85/≥130 mm Hg), fasting glucose ≥100 mg/dL or prevalent type 2 diabetes	N=75 6 weeks	Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions Secondary: Not reported	Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only reached significance in patients without small, dense LDL (P=0.043, P=0.006 and P=0.20). Reductions in TG were only significant with fluvastatin plus fenofibrate compared to ezetimibe plus simvastatin in patients with small, dense LDL (P=0.029). Increases in HDL-C and apo AI were only significant with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate in patients without small, dense LDL (P=0.020 and P=0.015). In patients with small, dense LDL, apo AII was markedly increased by fluvastatin plus fenofibrate, whereas ezetimibe plus simvastatin had no or little effect. Although only significant in small, dense LDL patients, apo CIII was more effectively reduce by fluvastatin plus fenofibrate, while the reduction of apo CII was more pronounced with ezetimibe plus simvastatin in all patients. Secondary: Not reported
Ballantyne et al.[71] (2007) EXPLORER Ezetimibe 10 mg QD and rosuvastatin 40 mg QD vs rosuvastatin 40 mg QD	MC, OL, PG, RCT Men and women aged ≥18 years with hypercholesterolemia, history of CHD or clinical evidence of atherosclerosis or CHD risk equivalent (10-year CHD risk score >20%), 2 most recent fasting LDL-C levels of ≥160 mg/dL and <250 mg/dL	N=469 6 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal (<100 mg/dL) after 6 weeks of treatment Secondary: Percentage of patients achieving the ATP III non-HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL, percentage	Primary: Significantly more patients in the combination therapy group achieved the LDL-C goal of <100 mg/dL at week six compared to rosuvastatin alone (94 vs 79.1%; P<0.001). Secondary: The non-HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL were achieved by a significantly higher percentage of patients in the combination therapy group than the monotherapy group (88 patients or 37.4% and 80 patients or 34.8%, respectively; P<0.001). There was a significantly higher percent of patients in the combination therapy group achieving the European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals (LDL <100 or 115 mg/dL and TC <175 or 190 mg/dL), depending on risk category compared to the rosuvastatin group alone at week six (LDL 93.6 vs 74.3%, LDL and TC 90.6 vs 68.3%, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of patients achieving the 2003 European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals of <100 or 115 mg/dL and <175 or 190 mg/dL, respectively, depending on risk category, percentage change from baseline in LDL, HDL, TC, TG, non-HDL, lipid ratios (LDL:HDL, TC:HDL and non-HDL:HDL), apo AI, apo B, and apo B:apo AI ratio, and changes in hsCRP in at week 6, safety and tolerability	At week six, the combination therapy group had a significantly greater percent reduction of 69.8% in the LDL level compared to a 57.1% reduction in the monotherapy group (P<0.001). Significantly greater reductions in TC, non-HDL-C and TG levels were seen in the combination group compared to the monotherapy group (P<0.001). Both treatment groups increased HDL level to a similar extent (P=0.151). LDL:HDL, TC:HDL and non-HDL:HDL cholesterol ratios decreased significantly more in patients receiving combination therapy compared to patients receiving monotherapy (all P<0.001). Significant decreases in apo B and the apo B:apo AI ratio were seen in the combination therapy group compared to the monotherapy group (P<0.001 for both). Apo AI increased by 3.2% and 1.6% in the combination therapy and monotherapy groups, respectively (P=0.202). The median percent decrease in CRP was significantly higher with combination therapy than monotherapy (-46.4 vs -28.6%; P<0.001). The overall frequency and type of adverse events were similar in both groups, with 31.5% of patients on combination therapy and 33.5% of patients on monotherapy reporting any adverse event. No adverse events were considered related to ezetimibe; the most frequently reported adverse event was myalgia (3.0% of patients in the rosuvastatin-alone group and 2.9% in the rosuvastatin plus ezetimibe group). There were two patients (0.8%) in the combination therapy group and three patients (1.3%) in the monotherapy group who discontinued the study due to treatment-related adverse events. One death occurred in the combination therapy group due to acute myocardial infarction and this was not considered to be related to study treatment. ALT increases >3 times the upper limit of normal were recorded in three patients, all in the combination therapy group.
Chenot et al.[72] (2007) Simvastatin 40 mg/day vs	RCT Patients, average age 61 years, admitted for an acute MI (with or without ST-segment elevation) to the coronary unit, with	N=60 7 days	Primary: Change from baseline in LDL-C at days 2, 4 and 7, and the achievement of LDL-C <70 mg/dL	Primary: Patients receiving ezetimibe plus simvastatin combination therapy experienced a statistically significant LDL-C reduction from baseline on days two, four, and seven (27, 41, and 51%, respectively; P<0.001). Patients on the simvastatin monotherapy experienced a statistically significant LDL-C reduction from baseline on days two, four, and seven (15, 27, and 25%, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ezetimibe 10 mg/day and simvastatin 40 mg/day vs no lipid-lowering therapy	pain that started within 24 hours of admission		Secondary: Not reported	There was no statistically significant change from baseline in LDL-C in the no lipid-lowering therapy group (P≥0.09). Patients on the ezetimibe plus simvastatin combination therapy achieved lower LDL-C levels compared to the simvastatin monotherapy group at day four (P=0.03) and day seven (P=0.002) of the study. A greater proportion of patients randomized to the ezetimibe plus simvastatin combination therapy achieved LDL-C <70 mg/dL, compared to the simvastatin monotherapy group at day four and day seven (45 vs 5, and 55 vs 10%, respectively). Secondary: Not reported
Gaudiani et al.[73] (2005) Simvastatin 20 mg/day and ezetimibe 10 mg/day vs simvastatin 40 mg/day All patients received simvastatin 20 mg/day for a 6 week run in period.	DB, MC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes (HbA_{1c} ≤9.0%), treated with a stable dose of pioglitazone (15 to 45 mg/day) or rosiglitazone (2 to 8 mg/day) for ≥3 months, LDL-C >100 mg/dL and TG <600 mg/dL (if already on a statin therapy)	N=214 30 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and apo AI	Primary: LDL-C was reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin (20.8 vs 0.3%; P<0.001). Secondary: TC (14.5 vs 1.5%; P<0.001), non-HDL-C (20.0 vs 1.7%; P<0.001), apo B (14.1 vs 1.8%; P<0.001), LDL-C:HDL-C (P<0.001), TC:HDL-C (P<0.001) and apo AI (P<0.001) were reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin. The increase in HDL-C was similar between the two treatments (P value not reported). The incidence of treatment-related adverse effects was lower with simvastatin compared to combination therapy (10.0 vs 18.3%, respectively; P value not reported).
Feldman et al.[74] (2004)	DB, MC, RCT Patients 18 to 80 years	N=710 23 weeks	Primary: Proportion of patients with LDL-	Primary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week five compared to patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg/day plus simvastatin 10, 20, or 40 mg/day vs simvastatin 20 mg/day	of age with CHD or CHD risk equivalent disease and LDL-C ≥130 mg/dL and TG ≤350 mg/dL		C <100 mg/dL at week five Secondary: Proportion of patients with LDL-C <100 mg/dL at 23 weeks	receiving simvastatin (P<0.001). Secondary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week 23 compared to patients receiving simvastatin (P<0.001). At five weeks, there was a significant reduction in TC, non-HDL-C, apo B, TC:HDL-C and LDL-C:HDL-C with combination therapy compared to simvastatin (P<0.001 for all). HDL-C was significantly increased with combination therapy (10/20 mg) compared to simvastatin (P<0.05). At five weeks, combination therapy was associated with a significant reduction in TG compared to simvastatin (P<0.05). Treatment-related adverse effects were similar with simvastatin and combination therapy (10/10, 10/20 and 10/40 mg) (7.5, 9.6, 14.0 and 10.0%, respectively; P values not reported).
Okada et al.[75] (2011) Ezetimibe 10 mg/day plus atorvastatin 10 mg/day vs ezetimibe 10 mg/day plus rosuvastatin 2.5 mg/day vs	MC, OL, PG, PRO, RCT Patients ≥20 years of age with CAD whose LDL-C levels were ≥100 mg/dL after ≥4 weeks of treatment with atorvastatin 10 mg/day or rosuvastatin 2.5 mg/day	N=171 12 weeks	Primary: Change from baseline in LDL-C, HDL, TG, TC, proportion of patients achieving an LDL-C <100 mg/dL Secondary: Not reported	Primary: In both the ezetimibe plus statin group and the double-dose statin group, LDL-C levels decreased from baseline to 12 weeks; however, the decrease was significantly greater in the ezetimibe plus statin group (24.7±12.1 vs -16.4±11.7%; P<0.01). The proportion of patients achieving the LDL-C goal of <100 mg/dL was significantly higher in the ezetimibe plus statin group compared to doubling the statin dose (76.1 vs 58.9%; P<0.05). The HDL-C level increased in the ezetimibe plus statin group and decreased in the double-dose statin group (2.7±16.6 vs -1.0±17.2%; P<0.05). The triglyceride level decreased for patients receiving ezetimibe plus a statin compared to an increase in triglycerides for patients who received an increased dose of statin (-9.4±30.2 vs 3.1± 40.7%, P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atorvastatin 20 mg/day vs rosuvastatin 5 mg/day				
Gagné et al.[76] (2002) Statin 40 mg for up to 14 weeks, followed by the addition of ezetimibe 10 mg QD for another 12 weeks, administered as separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily and addition of ezetimibe 10 mg QD daily for another 12 weeks, administered as separate vs statin 40 mg for up to 14 weeks,	DB, MC, RCT Patients ≥12 years old (or with body weight ≥40 kg) with hoFH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on atorvastatin or simvastatin 40 mg/day)	N=50 26 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (20.7 vs 6.7%; P=0.007). Secondary: TC was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (18.7 vs 5.3%; P<0.01). There was no statistically significant difference in any of the other secondary outcome measures between the two groups (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by titration to 80 mg daily Statins used in the study included simvastatin and atorvastatin.				
McKenney et al.[77] (2007) COMPELL Rosuvastatin 10 mg/day for 4 weeks, followed by 20 mg/day for 4 weeks, followed by 40 mg/day vs atorvastatin 20 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by atorvastatin 20 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day vs simvastatin 20	MC, OL, PG, RCT Patients ≥21 years of age with hyper-cholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL	N=292 12 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects	Primary: Atorvastatin plus niacin SR, rosuvastatin plus niacin SR, simvastatin plus ezetimibe and rosuvastatin were associated with similar reductions in LDL-C (56, 51, 57 and 53%, respectively; P=0.093). Secondary: Atorvastatin plus niacin SR was associated with a significant increase in HDL-C compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (22, 10 and 7%, respectively; P≤0.05). There was no significant differences in the reduction of non-HDL-C from baseline with any treatment (P=0.053). Atorvastatin plus niacin SR was associated with a significant reduction in TG compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (47, 33 and 25%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in Lp(a) compared to simvastatin plus ezetimibe and rosuvastatin (20 mg)-containing therapy (-14, 7 and 18%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in apo B compared to rosuvastatin (43 vs 39%, respectively; P≤0.05). Side effects were similar across treatments (P values not reported). There were no cases of myopathy or hepatotoxicity reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day plus ezetimibe 10 mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10 mg/day vs rosuvastatin 10 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by rosuvastatin 10 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by rosuvastatin 20 mg/day plus niacin SR 1,000 mg/day				
Trials Assessing Atherosclerosis Progression and Cardiovascular Outcomes				
Kastelein et al.[78] (2008) ENHANCE Ezetimibe 10 mg QD vs placebo All patients received	DB, MC, PC, PRO, RCT Men and women between the ages of 30 and 75 years with familial hypercholesterolemia regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C ≥210 mg/dL without	N=720 24 months	Primary Change in mean CIMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm with placebo and 0.0111±0.0038 mm with ezetimibe (P=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4 vs 45.3%; P=0.92) or new plaque formation (2.8 vs 4.7%; P=0.20) receiving placebo vs ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 and 0.0175±0.0049 mm, respectively; P=0.27).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin 80 mg QD.	treatment		patients with regression in the mean CIMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid artery IMT and average mean IMT of carotid and common femoral arteries, lipid parameters, CRP, adverse events	No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (P=0.93), carotid bulb (P=0.37), internal carotid artery (P=0.21) and femoral artery (P=0.16) or average of the mean values for carotid and femoral artery IMT (P=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the placebo group and by 55.6 mg/dL in the ezetimibe group (between-group difference of 16.5%; P<0.01). Reductions in TG (between-group difference of 6.6%; P<0.01) and CRP (between-group difference of 25.7%; P<0.01) were significantly higher with ezetimibe compared to placebo. Adverse events (29.5 vs 34.2%; P=0.18) and discontinuation rates (9.4 vs 8.1%; P=0.56) were similar between placebo and ezetimibe.
Rossebø et al.[79] (2008) SEAS Ezetimibe 10 mg QD and simvastatin 40 mg QD vs placebo OL lipid-lowering therapy, which included up to 40 mg of simvastatin or an equipotent dose of another	DB, MC, RCT Patients 45 to 85 years of age who had asymptomatic, mild-to-moderate aortic valve stenosis with a peak aortic-jet velocity of 2.5 to 4 m per second	N=1,873 52.2 months (median duration)	Primary: Composite of major cardiovascular events (death from cardiovascular causes, aortic-valve replacement, CHF as a result of progression of aortic-valve stenosis, nonfatal MI, hospitalization for unstable angina, CABG, PCI, non-hemorrhagic stroke)	Primary: The composite of major cardiovascular events occurred in 35.3% of patients in the simvastatin plus ezetimibe group and in 38.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.83 to 1.12; P=0.59). Secondary: There was no significant difference between the treatments in aortic-valve-related events (HR, 0.97; 95% CI, 0.83 to 1.14; P=0.73). Aortic-valve replacement occurred in 28.3% of patients in the simvastatin plus ezetimibe group and in 29.9% of patients in the placebo group (HR, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Ischemic cardiovascular events occurred in 15.7% of patients in the simvastatin plus ezetimibe group compared to 20.1% of patients in the placebo group (HR, 0.78; 95% CI, 0.63 to 0.97; P=0.02). A total of 7.3% of patients in the simvastatin plus ezetimibe group required CABG compared to 10.8% of patients in the placebo group (HR, 0.68; 95% CI, 0.50 to 0.93; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lipid-lowering drug, could be administered in addition to the study drug at the discretion of each treating physician.			Secondary: Aortic-valve events, progression of aortic stenosis, safety	There was no significant difference in the progression of aortic stenosis between the treatment groups. The mean peak aortic jet velocity was 3.71 m per second in the placebo group compared to 3.69 m per second in the simvastatin plus ezetimibe group at the end of the study (95% CI, -0.06 to 0.05; P=0.83). The mean pressure gradient increased to 34.4 mm Hg in the placebo group compared to 34.0±15.1 mm Hg in the simvastatin plus ezetimibe group at the end of the study. There was no significant difference in the aortic-valve area between the treatment groups. There was no significant difference in overall mortality among the treatment groups (P=0.80). The composite outcome of death from cardiovascular causes and the individual components of this composite outcome did not differ significantly between the two groups (P=0.34). There was a significant increase in the number of patients with elevated liver enzyme levels in the simvastatin plus ezetimibe group. There was also a higher incidence of cancer in the simvastatin plus ezetimibe group (11.1%) compared to placebo (7.5%; P=0.01).
Sampalis et al.[80] (2007) Ezetimibe 10 mg/day vs placebo All patients received statin therapy.	Post-hoc analysis Adult patients with hypercholesterolemia, with LDL-C levels exceeding the NCEP ATP goals on statin therapy	N=825 6 weeks	Primary: Reduction in the 10-year risk of CAD after six weeks Secondary: Not reported	Primary: The addition of ezetimibe to ongoing statin therapy was associated with a 25.3% reduction in the 10-year risk of CAD (P<0.001). Secondary: Not reported
Fleg et al.[81] (2008) SANDS	Subgroup analysis OL, RCT	N=427 3 years	Primary: CIMT after 36 months of	Primary: After 36 months, CIMT progressed in the standard group and regressed in the aggressive subgroups (ezetimibe plus statin and placebo; P<0.001 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD vs placebo All patients received aggressive statin therapy. Patients in the standard treatment arm served as the control group for this post-hoc analysis.	American Indian men and women ≥40 years of age with type 2 diabetes, LDL-C >100 mg/dL, SBP >130 mm Hg, and no prior cardiovascular events; this trial examined the effects of aggressive goals for LDL-C (<70 mg/dl), non-HDL-C (<100 mg/dL), and BP (<115/75 mm Hg) reduction vs standard goals of <100 mg/dL, <130 mg/dL, and <130/80 mm Hg, respectively.		treatment Secondary: Not reported	the standard group). There was a similar percent of patients in the aggressive treatment arms who demonstrated no change or a decrease in CIMT with ezetimibe plus statin compared to placebo (62 vs 61%, respectively). Only 39% of patients in the standard arm demonstrated no change or a decrease in CIMT (P<0.0001 vs the aggressive arm). Cardiovascular events occurred in 3.5, 5.8, and 3.3% of patients in the standard, aggressive with ezetimibe plus statin, and aggressive statin monotherapy subgroups (placebo), respectively (P=0.62). Secondary: Not reported
Taylor et al.[82] (2009) Ezetimibe 10 mg QD vs niacin SR (Niaspan®) 2 g (titrated) QD	OL, PG, RCT Patients ≥30 years of age with atherosclerotic coronary or vascular disease or a CHD risk equivalent (diabetes mellitus, 10-year Framingham risk score ≥20%, coronary calcium score >200 for women or >400 for men who were receiving treatment with a statin (LDL-C <100 mg/dL and HDL-	N=208 14 months	Primary: Change in CIMT after 14 months Secondary: Change in lipid values, composite of major adverse cardiovascular events (MI, myocardial revascularization, admission to the hospital for an acute coronary syndrome, and death from CHD),	Primary: Treatment with niacin led to a significant reduction in mean and maximal CIMT at eight months (P=0.001 and P=0.004, respectively) and 14 months (P=0.001 and P<0.001, respectively). There was no significant change in mean or maximal CIMT with ezetimibe at eight or 14 months compared to baseline. There was a significant difference between the niacin group and the ezetimibe group (P=0.003). Secondary: The change in LDL-C in the ezetimibe group was -17.6 mg/dL compared to -10.0 mg/dL in the niacin group (P=0.01). The change in HDL-C in the ezetimibe group was -2.8 mg/dL compared to 7.5 mg/dL in the niacin group (P<0.001). There were significant reductions in TG in both groups. Major adverse cardiovascular events occurred in 5% of patients receiving ezetimibe compared to 1% of patients receiving niacin (P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	C <50 mg/dL for men or <55 mg/dL for women)		discontinuation of study drug due to adverse effects, health-related quality of life	Adverse drug effects led to withdrawal from the study in three of nine patients receiving ezetimibe and 17 of 27 patients receiving niacin (P=0.12). There was no significant difference between the two groups in the quality of life at baseline or at 14 months.
Meaney et al.[83] (2009) VYCTOR Pravastatin 40 mg QD (ezetimibe 10 mg/day could be added if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions) vs simvastatin 40 mg QD (dose could be increased to 80 mg/day if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions) vs simvastatin-ezetimibe 20-10 mg QD (dose of	RCT, OL Patients 40 to 72 years of age with a 10-year absolute risk for coronary death or myocardial infarction ≥20 according to the ATP III recommendations	N=90 1 year	Primary: Change in CIMT Secondary: Changes in LDL-C and hsCRP	Primary: After one year, CIMT values were 0.93mm (-30%; P<0.01 vs baseline), 0.90 mm (-30%; P<0.01 vs baseline), and 0.92 mm (-25%; P<0.01 vs baseline) for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively. There was no significant difference among the treatment groups. Secondary: At the end of the study, LDL-C levels were 48, 45, and 48 mg/dL for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively (P<0.01 vs baseline for all). There was no significant difference among the treatment groups. The proportion of diabetic patients who attained LDL-C <70 mg/dL at the end of the trial were 62, 80, and 78% for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively (P values not significant). There was no significant difference among the treatment groups. There were no significant differences in hsCRP, HDL-C, TG among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin could be increased to 40 mg/day if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions)				

Drug regimen abbreviations: QD=once-daily, SR=sustained-release, XR=extended-release
Study abbreviations: AC=active comparator, DB=double=blind, DD=double dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, SB=single-blind, XO=cross-over
Miscellaneous abbreviations: apo=apolipoprotein, ALT=alanine aminotransferase, AST=aspartate aminotransferase, AVD=atherosclerotic vascular disease, BP=blood pressure, BMI=body mass index, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, CIMT=carotid intima-media thickness, CK=creatine kinase, CRP=C-reactive protein, FPG=fasting plasma glucose, HAART=highly active antiretroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, heFH=heterozygous familial hypercholesterolemia, HIV=human immunodeficiency virus, HR=hazard ratio, hoFH=homozygous familial hypercholesterolemia, hsCRP=high-sensitivity C-reactive protein, IDL-C=intermediate-density lipoprotein cholesterol, IMT=intima-media thickness, JBS2=Joint British Society 2, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MDA-LDL= malondialdehydemodified LDL, MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, PCI=percutaneous intervention, RLP-C=remnant-like particle cholesterol, RR=relative risk, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, US=United States,, VLDL-C=very low-density lipoprotein cholesterol, WMD=weighted mean difference

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Cholesterol Absorption Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ezetimibe	tablet	Zetia®	$$$$	N/A

N/A=Not available.

X. Conclusions

Ezetimibe is the only cholesterol absorption inhibitor in this class and it is not available in a generic formulation. It is approved for the treatment of primary hypercholesterolemia, mixed hyperlipidemia, homozygous familial hypercholesterolemia, and homozygous familial sitosterolemia.[1]

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When low-density lipoprotein lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing low-density lipoprotein cholesterol (LDL-C) levels, and are recommended in patients with established coronary heart disease or coronary heart disease equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant, niacin, or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy. With regards to the specific use of ezetimibe in lipid management, treatment guidelines recognize ezetimibe as a potential option to be added to statin therapy if lipid goals have not been met, or as a potential treatment option in patients who are unable to take statins, bile acid sequestrants, and/or niacin. Of note, the long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown.[3-8]

Clinical trials have demonstrated that monotherapy with ezetimibe significantly lowers total cholesterol, LDL-C, apolipoprotein B, and triglycerides, as well as increases high-density lipoprotein cholesterol compared to placebo.[1,21-26] The majority of available clinical trials evaluate ezetimibe as combination therapy with colesevelam, fenofibrates, niacin, and statins, and results demonstrate complementary effects on various lipid/lipoprotein parameters are achieved.[12-19,27-83] The effects of ezetimibe given either alone or in addition to a statin or fenofibrate on cardiovascular morbidity and mortality have not been established.[1] Ezetimibe should be available as adjunctive therapy through the medical justification portion of the prior authorization process.

Therefore, all brand cholesterol absorption inhibitors within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand cholesterol absorption inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Fibric Acid Derivatives
AHFS Class 240606
February 13, 2013

I. Overview

The antilipemic agents are categorized into five different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins), and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The fibric acid derivatives are agonists of the peroxisome proliferator activated receptor α (PPARα). Activation of PPARα increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of Apo CIII. The resulting decrease in triglycerides (TG) produces an alteration in the size and composition of low-density lipoprotein cholesterol (LDL-C) from small, dense particles to large buoyant particles. There is also an increase in the synthesis of high-density lipoprotein cholesterol (HDL-C), as well as apo AI and AII.[1-9] The fibric acid derivatives can decrease TG by 20 to 50% and increase HDL-C by 10 to 35%. They also lower LDL-C by 5 to 20%; however, in patients with hypertriglyceridemia, LDL-C may increase with the use of fibric acid derivatives.[10]

There are several fenofibrate products that are currently available, including micronized and non-micronized formulations. The different fenofibrate formulations are not equivalent on a milligram-to-milligram basis. Micronized fenofibrate is more readily absorbed than non-micronized formulations, which allows for a lower daily dose. Fenofibric acid is the active metabolite of fenofibrate.[11,12] Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available in a generic formulation.

The fibric acid derivatives that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. This class was last reviewed in August 2010.

Table 1. Fibric Acid Derivatives Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Fenofibrate	capsule, tablet	Lofibra®*, Lipofen®	fenofibrate
Fenofibrate, micronized	capsule	Antara®, Lofibra®*	fenofibrate, micronized
Fenofibrate, nanocrystallized	tablet	Tricor®*, Triglide®	fenofibrate, nanocrystallized
Fenofibric acid	delayed-release capsule, tablet	Fibricor®*, Trilipix®	fenofibric acid
Gemfibrozil	tablet	Lopid®*	gemfibrozil

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the fibric acid derivatives are summarized in Table 2.

Table 2. Treatment Guidelines Using the Fibric Acid Derivatives

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is

Clinical Guideline	Recommendation
Cholesterol Education Program Adult Treatment Panel III Guidelines[13] (2004)	advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on**	<u>General recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education

Clinical Guideline	Recommendation
Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report[10] (2002)	Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Statins</u> • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. <u>Bile acid sequestrants</u> • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. <u>Nicotinic acid</u> • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. <u>Fibric acid derivatives (fibrates)</u> • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. <u>Omega-3 fatty acids</u> • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses.

Clinical Guideline	Recommendation
	• In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update[14] (2011)**	Lipid management • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults[15] (2011)**	Clinical highlights • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures.

Clinical Guideline	Recommendation
	• Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established coronary artery disease, non-cardiac atherosclerosis, or coronary artery disease equivalent. Ongoing drug therapy • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30% reduction in CHD events. Monotherapy • Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy. • Specific statin and dose should be selected based on cost and amount of lipid-lowering required. • If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. • Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. • Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc). • Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin. • Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids

Clinical Guideline	Recommendation

	are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate).
	• Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease.
	• The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin.
	• The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown.
	• Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most potent with a statin.
	• Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after.
	
	<u>Combination therapy</u>
	• It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe.
	  ○ A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy.
	  ○ No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events.
	  ○ The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints.
	• Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy.
	• Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit.
	• There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins.
	• No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy.
	
	<u>Lifestyle modifications</u>
	• Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss.
	• Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range.

Clinical Guideline	Recommendation
	• A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended. • Vitamin E supplementation should not be used. • Light to moderate consumption of alcohol may lower CHD rates. • Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association[16] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice[17] (2012)**	Drugs • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. • Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. • Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. Drug combinations • Patients with dyslipidemia, particularly those with established CVD, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be

Clinical Guideline	Recommendation
	used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
National Institute for Health and Clinical Excellence: **Lipid Modification[18] (2010)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of cardiovascular disease for adults who have a ≥20% 10 year risk of developing cardiovascular disease. • Treatment for the primary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of cardiovascular disease. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of cardiovascular disease. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of cardiovascular disease. • Statin therapy is recommended for adults with clinical evidence of cardiovascular disease. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dL) or LDL-C <2 mmol/L (<77 mg/dL) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with cardiovascular disease who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[19] (2011)**	• Risk factor control for all patients with transient ischemic attack (TIA) or ischemic stroke: • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD. • For patients with atherosclerotic ischemic stroke or TIA without known CHD, it is reasonable to target a reduction of ≥50% in LDL-C or a target LDL-C level <70 mg/dL to obtain maximal benefit. • Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed

Clinical Guideline	Recommendation
	according to the National Cholesterol Education Program III guidelines (i.e., lifestyle modification, dietary guidelines, medication recommendations). • Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the fibric acid derivatives are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Fibric Acid Derivatives[1-9]

Indication	Fenofibrate	Fenofibric Acid	Gemfibrozil
Hypertriglyceridemia			
Adjunct to diet for treatment of adult patients with hypertriglyceridemia	✔ (Lofibra®)		
Adjunct to diet for treatment of severe hypertriglyceridemia	✔ (Antara®, Lipofen®, Tricor®, Triglide®)	✔ *	
Adjunct to diet for treatment of adult patients with very high elevations of serum triglyceride (TG) levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them			✔ †
Primary Hypercholesterolemia and Mixed Dyslipidemia			
Adjunct to diet to reduce elevated low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), TG, and apolipoprotein B (apo B), and to increase high density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia	✔ ‡	✔	
Adjunct to diet to reduce the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL-C and raise HDL-C) and who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated TG			✔
In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and coronary heart disease or a coronary heart disease risk equivalent who are on optimal statin therapy to achieve their LDL-C goal		✔ (Trilipix®)	

*Fibricor®: TG ≥500 mg/dL.
†Patients who present such risk typically have serum triglycerides over 2,000 mg/dl and have elevations of very low-density lipoprotein cholesterol (VLDL)-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Patients who consistently have total serum or plasma TG below 1,000 mg/dL are unlikely to present a risk of pancreatitis. Gemfibrozil may be considered for those patients with triglyceride elevations between 1000 and 2000 mg/dl who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis.

‡Antara® and Triglide®: when response to diet and nonpharmacological interventions alone has been inadequate.

IV. Pharmacokinetics

The pharmacokinetic parameters of the fibric acid derivatives are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Fibric Acid Derivatives[12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Fenofibrate	60 to 90	99	Liver (% not reported) Kidneys (% not reported)	Renal (60 to 93) Feces (5 to 25)	20 to 22
Fenofibric acid	81	99	Conjugation with glucuronic acid (% not reported)	Renal (primary; % not reported)	20
Gemfibrozil	Well absorbed (% not reported)	99	Liver (extensive; % not reported)	Renal (70) Feces (6)	1.5

V. Drug Interactions

Significant drug interactions with the fibric acid derivatives are listed in Table 5.

Table 5. Significant Drug Interactions with the Fibric Acid Derivatives[11]

Generic Name(s)	Significance Level	Interaction	Mechanism
Fenofibrate, Fenofibric acid, Gemfibrozil	1	Anticoagulants	Fibric acid derivatives may potentiate the inhibition of vitamin K dependent clotting factor synthesis by anticoagulants. The hypoprothrombinemic effect of anticoagulants may be increased by fibric acid derivatives and bleeding may occur.
Fenofibrate, Fenofibric acid, Gemfibrozil	1	Statins	The mechanism of interaction is not known. Severe myopathy may occur if fenofibrate and statins are coadministered.
Gemfibrozil	2	Repaglinide	Gemfibrozil may inhibit the metabolism of repaglinide, resulting in an increase in the plasma concentrations and the risk of severe and protracted hypoglycemia.
Gemfibrozil	2	Thiazolid-inediones	Gemfibrozil may inhibit the metabolism of thiazolidinediones, resulting in an increase in the plasma concentrations and pharmacologic effects of thiazolidinediones.

Significance Level 1 = major severity.
Significance Level 2 = moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the fibric acid derivatives are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Fibric Acid Derivatives[1-9,11,12]

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Cardiovascular			
Angina pectoris	✔	-	-
Arrhythmia	✔	-	-
Atrial fibrillation	✔	-	1
Cardiovascular disorder	✔	-	-
Coronary artery disorder	✔	-	-
Edema	✔	-	-
Electrocardiogram abnormal	✔	-	-
Hypertension	✔	✔	-
Hypesthesia	-	-	✔
Hypotension	✔	-	-
Migraine	✔	-	-
Myocardial infarction	✔	-	-
Palpitation	✔	-	-
Peripheral edema	✔	-	-
Peripheral vascular disorder	✔	-	✔
Phlebitis	✔	-	-
Syncope	-	-	✔
Tachycardia	✔	-	-
Varicose vein	✔	-	-
Vascular disorder	✔	-	-
Vasodilatation	✔	-	-
Ventricular extrasystoles	✔	-	-
Central Nervous System			
Anxiety	✔	-	-
Confusion	-	-	✔
Convulsion	-	-	✔
Depression	✔	-	✔
Dizziness	✔	3 to 4	✔
Fatigue	-	2 to 3	4
Fever	✔	-	-
Headache	3	12 to 13	1
Hypertonia	✔	-	-
Insomnia	✔	✔	-
Libido decreased	✔	-	✔
Nervousness	✔	-	-
Neuralgia	✔	-	-
Paresthesia	✔	-	✔
Pain	✔	-	-
Peripheral neuritis	-	-	✔
Somnolence	✔	-	✔
Vertigo	✔	-	2
Dermatological			
Acne	✔	-	-
Alopecia	✔	-	-
Angioedema	-	-	✔
Contact dermatitis	✔	-	-
Eczema	✔	-	2
Exfoliative dermatitis	-	-	✔
Fungal dermatitis	✔	-	-
Herpes simplex	✔	-	-
Herpes zoster	✔	-	-
Nail disorder	✔	-	-

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Maculopapular rash	✔	-	-
Photosensitivity reaction	✔	-	✔
Pruritus	✔	-	-
Rash	-	-	2
Skin disorder	✔	-	-
Skin ulcer	✔	-	-
Stevens-Johnson syndrome	✔	✔	-
Sweating	✔	-	-
Toxic epidermal necrolysis	✔	✔	-
Urticaria	✔	-	✔
Vasculitis	-	-	✔
Endocrine and Metabolic			
Diabetes mellitus	✔	-	-
Gout	✔	-	-
Gynecomastia	✔	-	-
Hypoglycemia	✔	-	-
Hyperuricemia	✔	-	-
Gastrointestinal			
Abdominal pain	5	✔	10
Anorexia	✔	-	-
Cholestatic jaundice	-	-	✔
Colitis	✔	-	-
Constipation	2	3	1
Diarrhea	2	3 to 4	7
Duodenal ulcer	✔	3 to 5	-
Dyspepsia	✔	-	20
Eructation	✔	-	-
Esophagitis	✔	-	-
Flatulence	✔	-	-
Nausea	2	4 to 6	2
Peptic ulcer	✔	-	-
Vomiting	✔	-	2
Weight gain/loss	✔	-	-
Genitourinary			
Creatinine increased	✔	-	-
Cystitis	✔	-	-
Decreased male fertility	-	-	✔
Dysuria	✔	-	-
Impotence	-	-	✔
Kidney function abnormal	✔	-	✔
Nephrotoxicity	✔	✔	✔
Prostatic disorder	✔	-	-
Unintended pregnancy	✔	-	-
Urinary frequency	✔	-	-
Urinary tract infection	-	✔	-
Vaginal moniliasis	✔	-	-
Hematologic			
Agranulocytosis	✔	✔	-
Anemia	✔	✔	✔
Ecchymosis	✔	-	-
Eosinophilia	✔	-	-
Hematocrit decreased	-	✔	-
Hemoglobin decreased	-	✔	-
Leukopenia	✔	✔	✔

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Lymphadenopathy	✔	-	-
Thrombocytopenia	✔	✔	✔
Hepatic			
Alkaline phosphokinase increased	-	-	✔
ALT increased	3	1 to 3	✔
AST increased	3	✔	✔
Bilirubin increased	-	-	✔
Cirrhosis	✔	✔	-
CPK increased	3	✔	✔
Hepatic enzymes increased	✔	✔	-
Hepatitis	✔	✔	-
Jaundice	-	-	✔
Liver fatty deposit	✔	-	-
Laboratory Test Abnormalities			
Serum creatinine increased	✔	✔	-
Musculoskeletal			
Arthralgia	✔	4	✔
Arthritis	✔	-	-
Arthrosis	✔	-	-
Bursitis	✔	-	-
Back pain	3	4 to 6	-
Joint disorder	✔	-	-
Leg cramps	✔	-	-
Muscle pain/spasm	✔	3 to 4	-
Myalgia	✔	3 to 4	-
Myasthenia	✔	-	✔
Myopathy	✔	-	✔
Myositis	✔	✔	-
Painful extremities	-	3 to 5	✔
Paresthesia	✔	-	✔
Rhabdomyolysis	✔	✔	✔
Synovitis	-	-	✔
Tenosynovitis	✔	-	-
Weakness	✔	✔	-
Respiratory			
Asthma	✔	-	-
Bronchitis	✔	✔	-
Cough	✔	✔	-
Dyspnea	✔	-	-
Laryngeal edema	-	-	✔
Laryngitis	✔	-	-
Nasopharyngitis	-	4 to 5	-
Pharyngitis	✔	-	-
Pneumonia	✔	-	-
Pulmonary embolism	✔	✔	-
Respiratory disorder	6	-	-
Rhinitis	2	-	-
Sinusitis	✔	3 to 4	-
Upper respiratory infection	-	4 to 5	-
Other			
Allergic reaction	✔	-	-
Amblyopia	✔	-	-
Anaphylaxis	-	-	✔
Appendicitis, acute	-	-	1

Adverse Events	Fenofibrate	Fenofibric Acid	Gemfibrozil
Asthenia	2	-	-
Blurred vision	-	-	✔
Cataracts	✔	-	✔
Chest pain	✔	-	-
Cholecystitis	✔	-	✔
Cholelithiasis	✔	✔	✔
Conjunctivitis	✔	-	-
Cyst	✔	-	-
Deep vein thrombosis	✔	✔	-
Drug-induced lupus syndrome	-	-	✔
Dry mouth	✔	-	-
Ear pain	✔	-	-
Eye disorder	✔	-	-
Flu syndrome	2	-	-
Hernia	✔	-	-
Hypersensitivity reaction	✔	✔	-
Infection	✔	-	-
Influenza	-	✔	-
Intracerebral hemorrhage	-	-	✔
Malaise	✔	-	-
Otitis media	✔	-	-
Pancreatitis	✔	✔	✔
Pharyngolaryngeal pain	-	✔	-
Raynaud's phenomenon	-	-	✔
Refraction disorder	✔	-	-
Retinal edema	-	-	✔
Seizure	-	-	✔
Syncope	-	-	✔
Taste perversion	-	-	✔
Vision abnormalities	✔	-	-

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the fibric acid derivatives are listed in Table 7.

Table 7. Usual Dosing Regimens for the Fibric Acid Derivatives[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Fenofibrate	<u>Hypertriglyceridemia:</u> Capsule (Antara®): 43 to 130 mg/day Capsule (Lofibra®): initial, 67 to 200 mg/day; maximum 200 mg/day Tablet (Lofibra®): initial, 54 to 160 mg/day; maximum, 160 mg/day <u>Primary hypercholesterolemia or mixed hyperlipidemia:</u> Capsule (Antara®): 130 mg/day Capsule (Lofibra®): initial, 200 mg/day; maximum 200 mg/day	Safety and efficacy in pediatric patients have not been established.	Capsule: 43 mg (Antara®) 50 mg (Lipofen®) 67 mg (Lofibra®) 130 mg (Antara®) 134 mg (Lofibra®) 150 mg (Lipofen®) 200 mg (Lofibra®) Tablet: 48 mg (Tricor®) 50 mg (Triglide®) 54 (Lofibra®) 145 mg (Tricor®) 160 mg (Lofibra®,

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Capsule (Lipofen®): 150 mg/day Tablet (Lofibra®): initial, 160 mg/day Tablet (Tricor®): initial, 145 mg once daily Tablet (Triglide®): 160 mg/day <u>Severe hypertriglyceridemia:</u> Capsule (Lipofen®): 50 to 150 mg/day Tablet (Tricor®): initial, 48 to 145 mg once daily; maximum, 145 mg/day Tablet (Triglide®): 50 to 160 mg/day		Triglide®)
Fenofibric acid	<u>Mixed hyperlipidemia:</u> Delayed-release capsule: initial, 135 mg once daily; maximum, 135 mg once daily <u>Primary hypercholesterolemia or mixed hyperlipidemia:</u> Tablet: 105 mg/day <u>Severe hypertriglyceridemia:</u> Delayed-release capsule: 45 to 135 mg once daily Tablet: 35 to 105 mg/day		Delayed-release capsule: 45 mg (Trilipix®) 135 mg (Trilipix®) Tablet: 35 mg (Fibricor®) 105 mg (Fibricor®)
Gemfibrozil	<u>Hypertriglyceridemia (very high elevations of serum triglyceride):</u> Tablet: 1,200 mg administered in two divided doses <u>Primary hypercholesterolemia or mixed hyperlipidemia:</u> Tablet: 1,200 mg administered in two divided doses		Tablet: 600 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the fibric acid derivatives are summarized in Table 8. Clinical trials have not been conducted with Lipofen®.[6] The pharmacological effects of fenofibric acid have been extensively studied through oral administration of fenofibrate, which is converted in vivo to fenofibric acid.[2]

Table 8. Comparative Clinical Trials with the Fibric Acid Derivatives

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Rosenson et al.[20] (2007) Fenofibrate 160 mg QD vs placebo	DB, PC, RCT Patients with fasting hypertriglyceridemia (≥1.7 and <6.9 mmol/L) and 2 or more of the NCEP ATP III criteria for the metabolic syndrome	N=59 19 weeks	Primary: Fasting TG, postprandial TG, oxidative stress, inflammatory response Secondary: Not reported	Primary: Fenofibrate treatment lowered fasting TG (-46.1%; P<0.0001) and postprandial (area under the curve) TG (-45.4%; P<0.0001) due to significant reductions in postprandial levels of large (-40.8%; P<0.0001), medium (-49.5%; P<0.0001) and VLDL particles. The number of fasting total LDL particles was reduced in fenofibrate-treated patients (-19.0%; P=0.0033) primarily due to reductions in small LDL particles (-40.3%; P<0.0001); these treatment differences persisted postprandially. Fasting and postprandial oxidized fatty acids were reduced in fenofibrate-treated patients compared to placebo-administered patients (-15.3%; P=0.0013, and 31.0%; P<0.0001, respectively). Fenofibrate therapy lowered inflammatory markers as follows: fasting and postprandial soluble VCAM-1 decreased by -10.9% for fasting VCAM-1 (P=0.0005), and by -12.0% for postprandial VCAM-1 (P=0.0001); and fasting and postprandial soluble ICAM-1 decreased by -14.8% for fasting ICAM-1 (P<0.0001) and by -15.3% for postprandial ICAM-1 (P<0.0001). Reductions in VCAM-1 and ICAM-1 were correlated with reductions in fasting and postprandial large VLDL particles (P<0.0001) as well as postprandial oxidized fatty acids (P<0.0005). Secondary: Not reported
Davidson et al.[21] (2006) TRIMS	DB, MC, PC, RCT Patients between the ages of 21 and 79	N=146 8 weeks	Primary: Changes or percent changes from baseline to the end-	Primary: There was a significant change from baseline in the mean percent decrease of TG in the fenofibrate group (36.6%) compared to essentially no change in the placebo group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fenofibrate 130 mg QD vs placebo	years, with fasting TG levels ≥300 and <1,000 mg/dL, and ≥2 of 4 additional components of the metabolic syndrome as defined by the NCEP ATP III		of-treatment in fasting TG Secondary: Changes or percent changes from baseline in TC, LDL-C, HDL-C, the TC:HDL-C ratio, VLDL-C, non-HDL-C; apo AI, B, and C-III; and remnant lipoprotein cholesterol	Secondary: There was no significant difference in TC change between the fenofibrate treatment and the placebo groups (P=0.085). LDL-C increased by a mean of 15.0% in the fenofibrate group compared to 3.2% in the placebo group (P=0.006). HDL-C increased by a mean of 14.0% in the fenofibrate group compared to 0.8% for placebo (P<0.001). The ratio of TC to HDL-C decreased with fenofibrate compared to placebo (-14.2 vs 0.8%; P<0.001). VLDL-C declined by 33% with fenofibrate compared to a 1.6% decline with placebo treatment (P<0.001). Non-HDL-C decreased significantly more in the fenofibrate group (-7.5 vs -1.1%; P=0.009). There was no significant difference in the rise in apo AI among the fenofibrate group vs the placebo response (5.3 vs 2.0%; P=0.212). Apo B declined significantly with fenofibrate compared to placebo (P<0.001, respectively). Apo CIII was markedly reduced in the fenofibrate group (P<0.001 compared to placebo). A significant reduction in remnant lipoprotein cholesterol was observed with fenofibrate treatment (-35.1 vs 12.3%; P<0.001).
Jones et al.[22] (2010) Fenofibric acid 135 mg/day vs	DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 and <400 mg/dL, HDL-C <40	N=543 12 weeks	Primary: Percentage changes from baseline in HDL-C and TG Secondary:	Primary: The addition of fenofibric acid resulted in a significantly greater mean percentage improvement in HDL-C (13.0 vs 4.2%; P<0.001) and TG (-57.3 vs -39.7%; P<0.001) compared to placebo. Secondary: The addition of fenofibric acid resulted in significantly greater effect on all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo All patients received atorvastatin 40 mg/day and ezetimibe 10 mg/day	mg/dL in men and <50 mg/dL in women and LDL-C ≥130 mg/dL)		Changes from baseline in apo AI, VLDL-C, apo CIII, non-HDL-C, apo B, hsCRP, LDL-C; proportion of patients achieving lipoprotein and apoprotein goals after 12 weeks of treatment; safety	secondary variables on non-HDL-C (P<0.001), apo B (P<0.001), apo AI (P=0.004), VLDL-C (P<0.001), apo CIII (P<0.001) and hsCRP (P<0.001) compared to placebo. The addition of fenofibric acid and placebo resulted in a >50% reduction in LDL-C (52.9 vs 52.0%; P value not reported), for final mean levels of 70.3 and 72.2 mg/dL. A numerically higher proportion of patients who added fenofibric acid achieved the LDL-C goal <100 mg/dL (92.7 vs 86.3%), the combined target of LDL-C <100 mg/dL and non-HDL-C <130 mg/dL (91.2 vs 84.0%) and the combined target of LDL-C <100 mg/dL, non-HDL-C <130 mg/dL and apo B <90 mg/dL (88.4 vs 80.8%) (P values not reported). Similar proportions of patients receiving both treatments achieved the LDL-C goal <70 mg/dL (55.0 vs 56.5%) and the combined target of LDL-C <70 mg/dL, non-HDL-C <100 mg/dL and apo B <80 mg/dL specified for high risk patients (53.4 vs 51.3%) (P values not reported). Both treatments were generally well tolerated. The percentages of patients discontinuing treatment were similar (9.6 vs 11.0%; P value not reported). The most common adverse events leading to discontinuations were myalgia and increases in ALT and/or AST. The treatments were similar in the incidence of adverse events experienced, treatment-related adverse events, serious adverse events and adverse events leading to withdrawal. The most commonly reported adverse events (≥3%) were muscle spasms, myalgia, arthralgia, fatigue, diarrhea, nausea, and headache.
Hogue et al.[23] (2008) Fenofibrate 200 mg QD vs atorvastatin 20 mg QD	RCT Patients with type 2 diabetes and hypertriglyceridemia	N=40 6 weeks	Primary: Lipids and TRL, inflammation and adhesion molecules Secondary: Not reported	Primary: Treatment with atorvastatin led to a significant decrease in plasma TC (-37.7%; P<0.0001), plasma TG (-37.6%, P<0.0001), plasma apo B (-43.2%, P<.0001), TRL-C (-44.1%, P<0.0001), TRL-TG (-36.9%, P<0.0001), TRL apo B (-13.8%, P=0.04), LDL-C (-43.0%, P<0.0001), LDL apo B (-42.7%, P<0.0001), and a significant increase in HDL-C (17.9%, P=0.001), and HDL apo A-I levels (10.3%, P=0.004). Treatment with fenofibrate led to a significant decrease in plasma C (-10.9%, P=0.0001), plasma TG (-41.4%, P=0.0002), plasma apo B (-9.9%, P=0.01), TRL-C (-52.8%, P<0.0001), TRL-TG (-46.3%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.0002), and TRL apo B (-14.8%, P=0.02) and a significant increase in LDL-C (15.9%, P=0.04) and HDL-C (8.9%, P=0.05). There were significant differences in the percentage changes of plasma cholesterol, plasma apo B, LDL-C, and LDL apo B between the two treatment groups. There was no significant difference in the percentage in changes of plasma TG between the treatment groups. Treatment with atorvastatin significantly decreased plasma levels of CRP (-26.9%, P=0.004), soluble ICAM-1 (-5.4%, P=0.03), soluble VCAM-1 (-4.4%, P=0.008), soluble E-selectin (-5.7%, P=0.02), MMP-9 (-39.6%, P=0.04), soluble phospholipase A2 (-14.8%, P=0.04), and oxidized LDL (-38.4%, P<0.0001). Fenofibrate significantly decreased soluble E-selectin levels only (-6.0, P=0.04) and increased soluble phospholipase A2 levels (22.5%, P=0.004). Secondary: Not reported
Arca et al.[24] (2007) Fenofibrate 200 mg/day vs atorvastatin 10 mg/day, titrated up to 80 mg/day	OL, RCT Patients 30 to 75 years of age with diagnosis of familial combined hyperlipidemia with TC and/or TG levels ≥90th Italian population percentiles, and/or hyper-apobeta-lipoproteinemia	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A and endothelin-1 Secondary: Not reported	Primary: Atorvastatin was associated with a significant 9% reduction in TC compared to fenofibrate (95% CI, 3.0 to 15.1; P=0.004). Atorvastatin was associated with a significant 17% reduction in LDL-C compared to fenofibrate (95% CI, 8.0 to 26.1; P<0.001). Fenofibrate was associated with a significant 15.5% reduction in TG compared to atorvastatin (95% CI, 3.35 to 27.70; P=0.013). Fenofibrate was associated with a significant 14.2% increase in HDL-C compared to atorvastatin (95% CI, 3.8 to 24.6%; P=0.008). Fenofibrate was associated with a significant 5.2 and 22.0% increase in apo AI and apo AII compared to atorvastatin (P=0.044 and P<0.001, respectively). Fenofibrate was associated with a significant 16.7% reduction in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				endothelin-1 from baseline (P<0.05). Atorvastatin was not associated with a significant change in endothelin-1 (P value not reported). Secondary: Not reported
Goldberg et al.[25] (2009) Fenofibric acid 135 mg QD plus atorvastatin 20 to 40 mg QD vs fenofibric acid 135 mg QD vs atorvastatin 20 to 40 mg QD	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 mg/dL, HDL-C <40 mg/dL for men and <50 mg/dL for women and LDL-C ≥130 mg/dL after lipid therapy washout)	N=613 12 weeks	Primary: Percent changes from baseline in TG, HDL-C and LDL-C Secondary: Percent changes from baseline in VLDL-C, TC, apo B and hsCRP; safety	Primary: Combination therapy (atorvastatin 20 mg) resulted in significantly greater improvements in TG (-45.6 vs -16.5%; P<0.001) and HDL-C (14.0 vs 6.3%; P=0.005) compared to atorvastatin 20 mg and LDL-C (-33.7 vs -3.4%; P<0.001) compared to fenofibric acid. Similarly, significantly greater improvements were observed with combination therapy (40 mg) in TG (-42.1 vs -23.2%; P<0.001) and HDL-C (12.6 vs 5.3%; P=0.010) compared to atorvastatin 40 mg and LDL-C (-35.4 vs -3.4%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (20 mg) resulted in significantly higher mean percentages of decrease in non-HDL-C compared to fenofibric acid (P=0.026) and in VLDL-C compared to atorvastatin 20 mg (P=0.046). Combination therapy (40 mg) also resulted in significantly higher mean percentage of decrease in non-HDL-C compared to fenofibric acid (P<0.001) and in VLDL-C compared to atorvastatin 40 mg (P<0.001). Improvements in other secondary variables were similar between combination therapy and atorvastatin (TC; P=0.688, apo B; P=0.688 and hsCRP; P=0.074).
Roth et al.[26] (2010) Rosuvastatin 5 mg/day vs fenofibric acid 135 mg/day	DB, MC, RCT Patients with fasting LDL-C ≥130 mg/dL, TG ≥150 mg/dL and HDL-C 40 mg/dL	N=760 12 weeks (plus a 30 day safety follow up period)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Changes from baseline in non-HDL-C, VLDL-C,	Primary: Combination therapy resulted in a significantly greater mean percent change in HDL-C (23.0 vs 12.4%; *P*<0.001) and TG (-43.0 vs -17.5%; *P*<0.001) compared to rosuvastatin, and resulted in significantly higher mean percent decrease in LDL-C compared to fenofibric acid (28.7 vs 4.1%; *P*<0.001). Secondary: Combination therapy resulted in significantly greater improvements in non-HDL-C compared to either monotherapy, and significantly greater improvements in apo B, hsCRP, VLDL-C and TC compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rosuvastatin 5 mg/day plus fenofibric acid 135 mg/day			apo B, hsCRP and TC; safety; proportion of patients achieving LDL-C (<100 mg/dL) and non-HDL-C (<130 mg/dL) goals	rosuvastatin. All treatments were generally well tolerated, with discontinuations due to adverse events being higher with combination therapy (8.3%) and fenofibric acid (7.5%) compared to rosuvastatin (4.4%). The most common adverse events leading to discontinuation were myalgia and muscle spasms and nausea, fatigue and ALT and AST increases. The overall incidence of treatment-emergent adverse events was similar across treatments (58.5 to 63.0%). No significant differences were observed between the combination therapy and either monotherapy in the incidence of any category of adverse events (muscle, hepatic and renal related). In patients with a 10 year CHD risk >20%, the LDL-C goal <100 mg/dL was achieved by 50.5% of patients receiving combination therapy and rosuvastatin; the non-HDL-C goal <130 mg/dL was achieved by 49.5% of patients receiving combination therapy compared to 33.3% of patients receiving rosuvastatin (*P*=0.03). Both LDL-C and non-HDL-C goals were achieved by 44.3 vs 32.3% (*P*=0.10).
Jones et al.[27] (2009) Fenofibric acid 135 mg QD and rosuvastatin (10 or 20 mg) QD vs fenofibric acid 135 mg QD vs rosuvastatin 10, 20, or 40 mg QD	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=1,445 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP	Primary: Combination therapy (rosuvastatin 10 and 20 mg) was associated with a significantly greater increase in HDL-C (10 mg: 20.3 vs 8.5%; P<0.001 and 20 mg: 19.0 vs 10.3%; P<0.001) and a significantly greater decrease in TG (10 mg: 47.1 vs 24.4%; P<0.001 and 20 mg: 42.9 vs 25.6%; P<0.001) compared to rosuvastatin (10 and 20 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (10 mg: 37.2 vs 6.5%; P<0.001 and 20 mg: 38.8 vs 6.5%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (rosuvastatin 10 mg) was associated with a significantly greater reduction in non-HDL-C compared to fenofibric acid or rosuvastatin (10 mg) (P<0.001). Combination therapy was also associated with significantly greater improvements in VLDL-C (P<0.001), apo B (P<0.001) and hsCRP (P=0.013) compared to rosuvastatin. Combination therapy (rosuvastatin 20 mg) significantly improved non-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				HDL-C compared to fenofibric acid (P<0.001) and was associated with a significantly greater improvement in VLDL-C (P=0.038) and hsCRP (P=0.010) compared to rosuvastatin (20 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
Ferdinand et al.[28] (2012) Fenofibric acid 135 mg QD and rosuvastatin 10 mg QD for 12 weeks, followed by fenofibric acid 135 mg QD and rosuvastatin 20 mg QD for up to 52 weeks Outcomes were evaluated from the end of the initial 12 week period (baseline) up to 52 weeks of treatment.	Post-hoc analysis Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=187 1 year	Primary: Change in baseline LDL-C, HDL-C, non-HDL-C, apo B, TG, hsCRP; proportion of patients achieving individual and combined goals for LDL-C and non-HDL-C; safety Secondary: Not reported	Primary: Increasing rosuvastatin from 10 to 20 mg, in combination with fenofibric acid for up to 52 weeks, resulted in significant changes from baseline in LDL-C (-9.5%), non-HDL-C (-0.6%), apoB (-8.5%), and HDL-C (3.6%) (P≤0.005 for all). TG levels remained unchanged (0.8%; P=0.055) at week 52. A greater proportion of patients achieved risk-stratified lipid goals at week 52 compared to baseline for LDL-C (89 vs 84%; P=0.26), non-HDL-C (50 vs 25%; P value not reported), and both LDL-C and non-HDL-C (50 vs 19%; P value not reported). The incidences of muscle-, hepatic-, and renal-related adverse events and laboratory values were within the expected range for combination therapy. The most commonly reported treatment-emergent adverse events (>10%) were upper respiratory tract infection (14.4%), headache (13.9%), and back pain (10.7%)/ Treatment-emergent serious adverse events occurred in seven percent of patients, and one death (MI) occurred, none of which were deemed to be treatment-related. Secondary: Not reported
Mohiuddin et al.[29] (2009) Fenofibric acid 135 mg QD plus simvastatin 20 to 40 mg QD vs fenofibric acid 135	AC, DB, MC Patients >18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, and LDL-C ≥130 mg/dL)	N=657 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in	Primary: Combination therapy was associated with a significantly greater increase in HDL-C (20 mg: 17.8 vs 7.2%; P<0.001 and 40 mg: 18.9 vs 8.5%; P<0.001) and a significantly greater decrease in TG (20 mg: 37.4 vs 14.2%; P<0.001 and 40 mg: 42.7 vs 22.4%; P<0.001) compared to simvastatin (20 and 40 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (20 mg: 24.0 vs 4.0%; P<0.001 and 40 mg: 25.3 vs 4.0%; P<0.001) compared to fenofibric acid.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QD vs simvastatin 20 to 80 mg QD			non-HDL-C, VLDL-C, TC, apo B and hsCRP	Secondary: Combination therapy (simvastatin 20 mg) was associated with a significantly greater decrease in non-HDL-C (P<0.001) compared to fenofibric acid and simvastatin (20 mg). Combination therapy (simvastatin 20 mg) was associated with significant improvements in VLDL-C (P<0.001), apo B (P<0.001) and hsCRP (P=0.013) compared to simvastatin (20 mg). Combination therapy (simvastatin 40 mg) significantly (P<0.001) improved non-HDL-C compared to fenofibric acid, and resulted in a significantly greater improvement in VLDL-C (P=0.005) compared to simvastatin (40 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
Derosa et al.[30](2009) Fenofibrate 145 mg/day and simvastatin 40 mg/day vs fenofibrate 145 mg/day vs simvastatin 40 mg/day	DB, MC, RCT Caucasian patients ≥18 years of age with type 2 diabetes mellitus and combined dyslipidemia who had never been treated with lipid-lowering medications	N=241 12 months	Primary: Lipid and lipoprotein profiles at six and 12 months Secondary: Not reported	Primary: After six months of therapy, there was a significant reduction in TC and LDL-C with simvastatin and fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively). There was no significant change in the fenofibrate group. After 12 months of therapy, there was a significant decrease in TC and LDL-C in all treatment groups (P<0.05 for fenofibrate, P<0.01 for the simvastatin and P<0.001 for fenofibrate plus simvastatin). TC was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). LDL-C was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.01). After six months of therapy, there was a significant reduction in TG with fenofibrate and fenofibrate plus simvastatin (P<0.05, respectively). There was no significant change in the simvastatin group. After 12 months of therapy, there was a significant decrease in TG in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate plus simvastatin). TG was significantly lower with fenofibrate + simvastatin compared to fenofibrate (P<0.05) or simvastatin (P<0.01). After six months of therapy, there was a significant increase in HDL-C with fenofibrate and fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively). There was no change in the simvastatin group. After 12

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				months of therapy, there was a significant increase in HDL-C in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate plus simvastatin). HDL-C was significantly higher with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). After six months of therapy, there was no significant change in apo A1 or apo B in any treatment group. After 12 months of therapy, there was a significant increase of apo A1 with fenofibrate plus simvastatin. There was no significant difference between the treatment groups. After 12 months of therapy, there was a significant decrease of apo B in all groups (P<0.05 for fenofibrate, P<0.05 for simvastatin and P<0.01 for fenofibrate plus simvastatin). There was no significant difference between the treatment groups. There were no significant differences in Lp(a) after six or 12 months of therapy in any of the treatment groups. After six months of therapy, there was a significant decrease in hsCRP with fenofibrate plus simvastatin (P<0.05), but not in the other groups. After 12 months of therapy, there was a significant decrease in hsCRP with simvastatin and with fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively), but not with fenofibrate. The hsCRP value was significantly lower with fenofibrate plus simvastatin compared to fenofibrate or simvastatin (P<0.05). Secondary: Not reported
May et al.[31] (2008) DIACOR Fenofibrate 160 mg and simvastatin 20 mg QD vs	DB, PC, RCT Patients with type 2 diabetes, no CHD, and biochemical evidence of mixed dyslipidemia (having 2 of the following 3 lipid parameters: LDL-C >100 mg/dL, TG >200 mg/dL, and	N=300 12 weeks	Primary: Lipid and lipoprotein profiles Secondary: Not reported	Primary: Fenofibrate plus simvastatin significantly reduced dense VLDL-C compared to fenofibrate (P<0.001) and simvastatin (P<0.0001). Simvastatin significantly reduced IDL-C compared to fenofibrate (P<0.003). The percentage of LDL-C pattern B constituting total LDL-C was significantly reduced by fenofibrate (-13.7%; P<0.0001) and fenofibrate plus simvastatin (-11.1%, P<0.0001). There was no significant change with simvastatin (-2.4%; P=0.27).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fenofibrate 160 mg QD vs simvastatin 20 mg QD	HDL-C <40 mg/dL)			Fenofibrate and fenofibrate plus simvastatin significantly increased the percentage of buoyant LDL-C constituting total LDL-C (-19.6%; P<0.0001 and -16.9%; P<0.0001, respectively). There was no significant change with simvastatin (-3.1%; P=0.06). Secondary: Not reported
Jones et al.[32] (2009) Fenofibric acid 135 mg QD vs low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs fenofibric acid 135 mg plus low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs moderate-dose statin (rosuvastatin 20 mg, simvastatin	Pooled analysis of 3 AC, DB, MC, RCT Patients >18 years of age, with HDL-C <40 mg/dL (men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL ≥130 mg/dL	N=2,715 12 weeks	Primary: Mean percent change in HDL-C, TGs (fenofibric acid plus atorvastatin vs atorvastatin), and LDL-C (fenofibric acid plus atorvastatin vs fenofibric acid) Secondary: Mean percent change in non-HDL-C, VLDL-C, TC, apo B, and hsCRP; safety	Primary: Fenofibric acid plus low-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (18.1 vs 7.4%; P<0.001) and a greater mean percent decrease in TG (-43.9 vs -16.8%; P<0.001) compared to low-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-33.1 vs -5.1%; P<0.001) compared to fenofibric acid monotherapy. Fenofibric acid plus moderate-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (17.5 vs 8.7%; P<0.001) and a greater mean percent decrease in TG (-42.0 vs -23.7%; P<0.001) compared to moderate-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-34.6 vs -5.1%; P<0.001) compared to fenofibric acid monotherapy. No formal comparisons were made between the high-dose statin monotherapy group and the other treatment groups. Secondary: Greater improvements in non-HDL-C, VLDL-C, TC, and apo B were observed for fenofibric acid plus low-dose statin combination therapy compared to corresponding monotherapies (P≤0.001). Combination therapy was generally well tolerated, and safety profiles were similar to monotherapies. No rhabdomyolysis was reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40 mg, or atorvastatin 40 mg) QD vs fenofibric acid 135 mg QD plus moderate-dose statin QD vs high-dose statin (rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg) QD				
Bays et al.[33] (2008) Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) Extension study patients received the same type of statin that was used in the statin-containing arms of the controlled	MC, OL Patients with mixed dyslipidemia completing 1 of 3 MC, PRO, DB, RCT 12-week studies were eligible	N=2,201 1 year	Primary: Safety, percent changes from baseline in TG, HDL-C, and LDL-C Secondary: Percent changes in non-HDL-C, VLDL-C, TC, apoB, and hs-CRP	Primary: Of the 2,201 patients who received at least one dose of fenofibric acid plus statin combination therapy, six patients (0.3%) died during the conduct of the ES; no death was considered by the investigator to be treatment related. Overall, 148 (6.7%) patients had treatment-emergent serious adverse events (fenofibric acid plus rosuvastatin, 7.2%; fenofibric acid plus simvastatin, 7.8%; fenofibric acid + atorvastatin 4.6%). The most common treatment-emergent serious adverse events were osteoarthritis, deep vein thrombosis, CAD, MI, and chest pain, diverticulitis, syncope, and intervertebral disc protrusion. A total of 1,856 patients (84.3%) had one or more treatment-emergent adverse events (fenofibric acid plus rosuvastatin, 83.1%; fenofibric acid plus simvastatin, 86.2%; fenofibric acid plus atorvastatin, 85.2%). The most frequently reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, and back pain.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
study in which they participated				Among patients who received fenofibric acid monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-22.0%), mean percent decrease in LDL-C (-38.1%), and mean percent increase in HDL-C (6.2%). Among patients who received moderate-dose statin monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-30.5%) and mean percent increases in HDL-C (13.1%) and LDL-C (3.1%). Among patients who received fenofibric acid plus low-dose statin combination therapy in a controlled study, there was an additional median percent decrease in TG (-4.2%), mean percent increase in HDL-C (4.8%), and mean percent decrease in LDL-C (-9.7%) after the statin dose was increased for 52 weeks. The group of patients who were treated with fenofibric acid plus moderate-dose statin in a controlled study and continued the same therapy in the extension study exhibited sustained improvements in lipid parameters throughout the course of therapy. For this group of patients, treatment with fenofibric acid plus moderate-dose statin combination therapy for a total of 64 weeks decreased TG from a mean baseline of 297.8 mg/dL to a mean final level of 138.0 mg/dL, decreased LDL-C from a mean baseline of 153.1 mg/dL to a mean final level of 94.2 mg/dL, and increased HDL-C from a mean baseline of 38.2 mg/dL to a mean final level of 47.7 mg/dL. Secondary: Among patients who received fenofibric acid monotherapy or moderate-dose statin monotherapy in the controlled studies, treatment with fenofibric acid plus moderate-dose statin combination therapy in the extension study resulted in additional mean percent decreases in non-HDL-C, VLDL-C, TC, and apo B, and median percent decrease in hsCRP that were sustained throughout 52 weeks of combination therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For patients initially treated with fenofibric acid plus low-dose statin combination therapy, increasing the statin dose resulted in additional mean percent decreases in non-HDL-C, TC, and apo B and median percent decrease in hsCRP, which were sustained throughout the study.
Kipnes et al.[34] (2010) Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) ES patients received the same type of statin that was used in the statin-containing arms of the controlled study in which they participated.	ES, OL Patients with mixed dyslipidemia at the start of a 1 year, ES, OL	N=310 1 year (2 years of total therapy)	Primary: Safety and efficacy Secondary: Not reported	Primary: No deaths occurred during the two year trial. The incidence of serious adverse events was numerically highest with fenofibric acid plus rosuvastatin (14.9%) compared to fenofibric acid plus simvastatin (8.0%) or atorvastatin (5.8%). The incidences of adverse events were similar among all treatments as well (94.8, 90.0 and 97.7%). Adverse events tended to occur early in treatment, without the development of new types of adverse events over time. The most common treatment-related adverse events were muscle spasms (3.9%), increased blood creatine phosphokinase (3.5%), headache (2.9%), myalgia (2.9%), dyspepsia (2.3%) and nausea (2.3%). Rhabdomyolysis was not reported with any treatment. Nine patients discontinued therapy due to adverse events, with similar incidences among all treatments. Myalgia was the most common reason for discontinuation. No significant difference in the incidence of laboratory elevations was observed among the treatment groups. Incremental improvements in mean percentage changes in all efficacy variables were observed after the first visit in the year one ES (week 16). This effect was sustained for greater than two years and sizable mean percentage changes in all efficacy variables were observed at week 116. In the overall population, the mean percentage changes from baseline to week 116 in efficacy variables were: 17.4 (HDL-C), -46.4 (TG), -40.4 (LDL-C), -47.3 (non-HDL-C), -37.8 (TC) and -52.8% (VLDL-C). Significant differences among treatments were observed for non-HDL-C (-48.60±13.58 vs -41.70±13.10 vs -47.30±12.50%; *P*=0.011), TC (-38.70±12.16 vs -32.50±10.86 vs -38.60±10.85%; *P*=0.007) and VLDL-C (-56.80±25.17 vs -40.30±51.25 vs -51.20±35.42%; *P*=0.019). Secondary: Not reported
Farnier et al.[35] (2005)	DB, MC, PC, RCT Men and women 18	N=619 12 weeks	Primary: Percent change in LDL-C from	Primary: The mean percent change in LDL-C reduction was significantly greater in the micronized fenofibrate and ezetimibe group when compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs ezetimibe 10 mg QD vs placebo	to 75 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or 10-year CHD risk >20%		baseline to study end point Secondary: Percent change in other lipid, non-lipid, and lipoprotein parameters from baseline to study end point	other treatment groups (P<0.001 compared to micronized fenofibrate and ezetimibe). These reductions were 13.4% in the ezetimibe group, 5.5% in the micronized fenofibrate group, and 20.4% in the micronized fenofibrate and ezetimibe group. Secondary: When compared to micronized fenofibrate or ezetimibe monotherapy, significant reductions in apo B, non-HDL-C and LDL-C were observed in the micronized fenofibrate and ezetimibe group; P<0.001. When compared to placebo, significant decreases in TG levels and significant increases in HDL-C level were observed in both the micronized fenofibrate plus ezetimibe and micronized fenofibrate treatment groups; P<0.001. The percent changes from baseline to study end point were as follows: -11.8% in TC, 3.9% in HDL-C, -11.1% in TG, and -6.1% in hsCRP in the ezetimibe group; -10.8% in TC, 18.8% in HDL-C, -43.2% in TG, and -28.0% in hsCRP in the micronized fenofibrate group; -22.4% in TC, 19.0% in HDL-C, -44.0% in TG, and -27.3% in hsCRP in the micronized fenofibrate and ezetimibe group (P<0.05 for all).
Tribble et al.[36] (2008) Ezetimibe 10 mg and fenofibrate 160 mg QD (FENO + EZE) vs ezetimibe 10 mg QD (EZE) vs fenofibrate 160 mg QD (FENO)	DB, MC, PC, RCT Patients 18 to 75 years of age with mixed hyperlipidemia (LDL-C 130 to 220 mg/dL and TG 200 to 500 mg/dL) and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=625 12 weeks	Primary: Changes in cholesterol mass within the major lipoprotein fractions and subfractions and LDL particle distribution profiles and particle size Secondary: Not reported	Primary: The effects of EZE, FENO, and FENO + EZE on VLDL subfractions were similar to those for VLDL overall. All active treatments reduced IDL-C. Treatment with FENO significantly reduced LDL-C1, LDL-C3, and LDL-C4 and significantly increased LDL-C2 compared to placebo. FENO + EZE produced a pattern of changes similar to those of FENO alone. The reductions in LDL-C1 and LDL-C3 were greater with the combination due to the added effects of EZE. There were no significant changes in cholesterol associated with Lp(a). Fenofibrate and FENO + EZE increased median HDL-C2 and HDL-C3 compared to EZE and placebo. In patients treated with EZE, there were reductions in VLDL-C, IDL-C, and LDL-C density ranges without a shift in LDL density distributions or

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				changes in the HDL-C range. In patients treated with FENO, there were reductions in VLDL-C and IDL-C. HDL-C was increased and there was a shift in the distribution of LDL toward larger, more buoyant LDL particles with a small effect on LDL-C values overall. In patients treated with FENO + EZE, there were reductions in VLDL-C, IDL-C, and LDL-C. HDL-C was increased and there was a shift from smaller, more dense to larger, more buoyant LDL subfractions. EZE did not significantly affect LDL peak particle size. FENO and FENO + EZE increased LDL peak particle size. Secondary: Not reported
McKenney et al.[37] (2006) Fenofibrate 160 mg QD and ezetimibe 10 mg QD vs fenofibrate 160 mg QD vs ezetimibe 10 mg QD for 12 weeks, then fenofibrate 160 mg and ezetimibe 10 mg QD for 48 weeks	DB Patient who completed base study with mixed hyperlipidemia	N=576 48 weeks	Primary: Percent change in LDL-C from baseline of the base study to study end point in the extension Secondary: Percent change from baseline to study end point in TC, HDL-C, TG, non-HDL-C, apo B, apo AI, and hsCRP	Primary: Fenofibrate plus ezetimibe showed significantly greater percent reductions in LDL-C compared to fenofibrate alone (-22.0 vs -8.6; P<0.001). Secondary: Fenofibrate plus ezetimibe showed significantly greater percent reductions from baseline to extension study end point in TC (-23.2 vs -13.6; P<0.001), TG (-46.0 vs -41.0; P=0.002), non-HDL-C (-31.6 vs -19.4; P<0.001), and apo B (-25.2 vs -16.2; P<0.001) compared to fenofibrate. There was a significantly greater percent increase in HDL-C (20.9 vs 17.8; P=0.02) with fenofibrate plus ezetimibe vs fenofibrate alone. There was not a significantly greater percent increase in apo AI (10.1 vs 7.8; P=0.12) with fenofibrate plus ezetimibe vs fenofibrate alone. Reductions in median hsCRP levels were not different between treatments (-25.3 vs -21.1; P=0.46) for fenofibrate plus ezetimibe vs fenofibrate alone, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 12 weeks, then fenofibrate 160 mg for 48 weeks				
Ansquer et al.[38](2009) Fenofibrate (Tricor®) 145 mg and ezetimibe 10 mg QD vs fenofibrate (Tricor®) 145 mg QD vs ezetimibe 10 mg QD	DB, MC, RCT Patients 18 to 70 years of age with type IIb dyslipidemia (LDL-C ≥160 mg/dL, TG 150 to 405 mg/dL) and ≥2 features of the metabolic syndrome according to the NCEP ATP III definition	N=60 12 weeks	Primary: Percentage change from baseline in TG and HDL-C Secondary: Percentage change in LDL-C, non-HDL-C, remnant-like particle cholesterol (RLP-C) and related parameters, change in glucose metabolism parameters, hsCRP, safety	Primary: Fenofibrate plus ezetimibe and fenofibrate reduced TG by -38.3% (P value not significant) and increased HDL-C to a similar extent (11.5 and 7.9%, respectively; P=0.282). Secondary: Fenofibrate plus ezetimibe reduced LDL-C by -36.2% compared to -22.4% with fenofibrate and -22.8% with ezetimibe (P<0.001 for both). Fenofibrate plus ezetimibe lowered non-HDL-C by -36.2% compared to fenofibrate (-24.8%) and ezetimibe (-20.9%) (P value not reported). There was no significant difference between fenofibrate plus ezetimibe and fenofibrate with regards to RLP-C (-36.2 vs -30.7%; P value not significant). Ezetimibe was less effective than fenofibrate plus ezetimibe (-17.3%; P<0.001). The effect of fenofibrate plus ezetimibe on LDL particle size (+2.1%) was similar to that of fenofibrate (+1.9%). Fenofibrate plus ezetimibe was more effective than monotherapy with fenofibrate or ezetimibe in reducing apo B (-33.3%). Fenofibrate plus ezetimibe had the same effect as fenofibrate on apo AI (+7.9 vs +5.1%, respectively) and apo AII (+24.2 vs +21.2%, respectively; P value not reported). Fenofibrate plus ezetimibe and fenofibrate reduced hsCRP to a similar degree.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a higher incidence of treatment-related adverse events with fenofibrate/ezetimibe, which was primarily due to abnormal laboratory changes, including moderate increases in CK, liver enzymes, and blood creatinine.
Farnier et al.[39] (2007) Fenofibrate 160 mg QD and simvastatin-ezetimibe 20-10 mg QD vs fenofibrate 160 mg QD vs simvastatin-ezetimibe 20-10 mg QD vs placebo	DB, MC, PA, PC, RCT Patients 18 to 79 years old with mixed hyperlipidemia and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in TC, TG, HDL-C, non-HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C/HDL-C, apo B	Primary: Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction in LDL-C from baseline compared to the fenofibrate monotherapy group (45.8 vs 15.7%; P<0.05). There was no significant difference between LDL-C reduction seen with the simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (45.8 vs 47.1%; P>0.2). Secondary: Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction from baseline in non-HDL-C, TG, and apo B compared to the other treatment groups (P<0.01). There was no significant difference between TC reduction seen with the simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (38.7 vs 35.4%; P>0.05). Simvastatin-ezetimibe plus fenofibrate group exhibited significant increase from baseline in HDL-C compared to the simvastatin-ezetimibe group (18.7 vs 9.3%; P<0.01). Simvastatin-ezetimibe plus fenofibrate group exhibited significant reduction from baseline in LDL-C:HDL-C, TC:HDL-C compared to the simvastatin-ezetimibe group (P=0.03). There was no significant difference between the percentage of patients able to reach their LDL-C goal with the simvastatin-ezetimibe plus fenofibrate therapy and simvastatin-ezetimibe therapy (88.5 vs 92.9%).
Farnier et al.[40] (2008) Fenofibrate 160	RCT, DB, MC, PC Patients 18 to 79 years of age with	N=611 12 weeks	Primary: Percent change in cholesterol associated with	Primary: The effects of ezetimibe-simvastatin, fenofibrate, and ezetimibe/simvastatin plus fenofibrate on VLDL subclasses were similar to those for VLDL-C overall.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg and ezetimibe-simvastatin 10-20 mg QD vs fenofibrate 160 mg QD vs ezetimibe-simvastatin 10-20 mg QD vs placebo	mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or CHD risk score >20% (as defined by NCEP ATP III), LDL-C 130 to 220 mg/dL and TG 150 to 500 mg/dL		lipoprotein subfractions (VLDL-C 1+2 and VLDL-C 3, IDL-C, LDL-C 1 to 4, Lp[a], $HDL\text{-}C_2$ and $HDL\text{-}C_3$, and changes in LDL particle size) Secondary: Not reported	The maximal changes in IDL-C are achieved by ezetimibe-simvastatin with little additional effect of fenofibrate. Significant reductions were observed for all LDL-C subfractions with ezetimibe-simvastatin treatment. When coadministered with fenofibrate, the effects of both treatments were evident. Ezetimibe-simvastatin plus fenofibrate resulted in a pattern of changes that were similar to fenofibrate monotherapy indicating that the change in LDL-C pattern was primarily a function of fenofibrate. There was no significant difference in cholesterol associated with Lp(a) among the treatment groups. Fenofibrate and ezetimibe-simvastatin plus fenofibrate led to similar increases in median $HDL\text{-}C_2$ and $HDL\text{-}C_3$ compared to ezetimibe-simvastatin and placebo. Ezetimibe-simvastatin did not significantly affect LDL particle size. Fenofibrate and ezetimibe-simvastatin plus fenofibrate increased LDL particle size. At the end of the study, the percentages of patients exhibiting LDL size pattern B was 64, 49, 14, and 17% in the placebo, ezetimibe-simvastatin, fenofibrate, and ezetimibe-simvastatin plus fenofibrate groups, respectively. Secondary: Not reported
Kumar et al.[41] (2009) Ezetimibe 10 mg/day plus fenofibrate 160 mg/day vs	RCT, XO Patients with hypercholesterolemia requiring pharmacotherapy	N=43 12 weeks	Primary: Percentage reduction of LDL-C Secondary: Percent changes from baseline in TC, HDL-C and TG	Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (P=0.46). Secondary: Both treatments provided similar improvements in TC (-25.1 vs -24.6%; P=0.806) and HDL-C (10.1 vs 8.9%; P=0.778). Combination therapy showed a trend towards a greater reduction in TGs (25.4 vs 14.5%; P=0.079), although there were no significant difference between the two treatments in terms of the improvement in TC:HDL-C (-29.0 vs -28.7%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
atorvastatin 10 mg/day				P=0.904).
Winkler et al.[42] (2009) Fluvastatin 80 mg/day plus fenofibrate 200 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 mg/day	MC, OL, RCT, XO Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist circumference ≥94 (men) or ≥80 cm (females) plus 1 of the following: TG ≥150 mg/dL, BP (≥85/≥130 mm Hg), FPG ≥100 mg/dL or prevalent type 2 diabetes	N=75 6 weeks	Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions Secondary: Not reported	Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only reached significance in patients without small, dense LDL (P=0.043, P=0.006 and P=0.20). Reductions in TG were only significant with fluvastatin plus fenofibrate compared to ezetimibe plus simvastatin in patients with small, dense LDL (P=0.029). Increases in HDL-C and apo AI were only significant with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate in patients without small, dense LDL (P=0.020 and P=0.015). In patients with small, dense LDL, apo AII was markedly increased by fluvastatin plus fenofibrate, whereas ezetimibe plus simvastatin had no or little effect. Although only significant in small, dense LDL patients, apo CIII was more effectively reduce by fluvastatin plus fenofibrate, while the reduction of apo CII was more pronounced with ezetimibe plus simvastatin in all patients. Secondary: Not reported
Wi et al.[43] (2010) Niacin ER 500 mg/day for 5 weeks, followed by 1,000 mg/day for 4 weeks, followed by 1,500 mg/day vs fenofibrate 160 mg/day After	OL, RCT Patients 20 to 79 years of age with TG 150 to 499 mg/dL and HDL-C <45 mg/dL	N=201 24 weeks (includes 8 week dietary run in period)	Primary: Percent change from randomization to week 16 in apo B/apo AI Secondary: Percent changes in other lipid parameters, levels of glucose metabolism-related parameters, hsCRP	Primary: Apo B/apo AI was reduced with both treatments with no difference between the two (P=0.47). The percent reduction in apo B was greater with niacin, whereas the percent elevation in apo AI was higher with fenofibrate. Secondary: TC significantly decreased with both treatments, and TG decreased and HDL-C increased. LDL-C increased with fenofibrate but decreased with niacin. The percent reduction in TC was greater with niacin (P=0.01). TG decreased significantly more with fenofibrate (P=0.045), whereas the percent elevation in HDL-C was not different between the two treatments (P=0.22). The percent change in LDL-C was significantly different with the two treatments (P<0.001). Lp(a) levels were reduced with niacin only, and the change was significantly different compared to fenofibrate (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
discontinuation of any lipid modifying drug, patients entered an 8 week dietary run in period.				FPG levels decreased with fenofibrate and increased significantly with niacin. HbA_{1c} levels increased with both treatments; the increase was borderline with fenofibrate and significant with niacin. The percent changes in FPG (P<0.001) and HbA_{1c} (P<0.001) levels were significantly different between the two treatments. Fasting insulin levels showed a borderline reduction with fenofibrate and a significant increase with niacin. HOMA-IR was decreased with fenofibrate and was increased with niacin. Percent changes of insulin (P<0.001) and HOMA-IR (P<0.001) were significantly different between the two treatments. hsCRP levels were significantly lowered with both treatments, but the percent change was greater with niacin (P=0.03).
Alrasadi et al.[44] (2008) <u>Protocol 1</u> Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID for 8 weeks <u>Protocol 2</u> Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	N=19 32 weeks	Primary: Percent changes in HDL-C and TC/HDL-C ratio Secondary: Not reported	Primary: <u>Protocol 1</u> The mean percent change in HDL-C was +6, -6, and +22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +19, -26, and -22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). <u>Protocol 2</u> The mean percent change in HDL-C was -2 and +18% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +32 and -32% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC/HDL-C (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs niacin SR 1 g BID and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study in Protocol 2.				
Balasubramanyam et al.[45] (2011) Usual care vs low saturated fat diet and exercise (D/E) vs D/E and fenofibrate 145 mg/day (Tricor®) vs D/E and niacin SR	DB, PC, RCT Patients 21 to 65 years of age with hypertriglyceridemia (fasting TG >150 mg/dL) and receiving stable ART therapy for 6 months	N=191 24 weeks	Primary: Baseline changes in lipid parameters Secondary: Baseline changes in insulin sensitivity, glycemia, adiponectin, CRP, energy expenditure, and body composition	Primary: Patients receiving fenofibrate achieved significant improvements in TG (P=0.002), TC (P=0.02), and non-HDL-C (P=0.003), compared to patients receiving niacin who achieved significant improvements in HDL-C (P=0.03), and both groups of patients achieved significant improvements in TC:HDL-C (P=0.005 and P=0.01). The combination of D/E plus fenofibrate plus niacin provided maximal benefit, reducing TG (-52% vs usual care; P=0.003), increasing HDL-C (12% vs usual care; P<0.001), and decreasing non-HDL-C (-18.5% vs usual care; P=0.003) and TC:HDL-C (-24.5% vs usual care; P<0.001). Secondary: Of the secondary endpoints evaluated, there was an effect of niacin on FPG (P=0.0002), oral glucose tolerance test area under the curve for glucose (P=0.02), fasting insulin (P=0.03), HOMA-IR (P=0.008), insulin sensitivity index (P=0.007), and adiponectin (P<0.0001), and an effect of fenofibrate on creatinine (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2,000 mg/day (Niaspan®) vs D/E and fenofibrate 145 mg/day and niacin SR 2,000 mg/day				
Roth et al.[46] (2009) Phase I Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks vs fenofibrate 130 mg (FENO) QD and placebo for 8 weeks Phase II Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks	DB, MC, PC, RCT Patients 18 to 79 years of age with Fredrickson type IV dyslipidemia, BMI 25 to 43 kg/m^2, and TG 500 to 1,300 mg/dL	N=167 16 weeks	Primary: Median percent change in TG Secondary: Additional lipid and cardiovascular risk factors	Primary: After eight weeks of therapy, median TG values were reduced from 649.5 to 267.5 mg/dL (-60.8%) with P-OM3 + FENO and from 669.3 to 310 mg/dL (-53.8%) with FENO monotherapy (P=0.059). There was no significant difference between the treatment groups (P=0.059). Secondary: LDL-C was significantly increased with P-OM3 + FENO compared to FENO monotherapy (48.2 vs 39.0%, respectively; P=0.030). There was no significant difference in non-HDL-C among the treatment groups (-8.2% for P-OM3 + FENO vs -7.1% for FENO; P=0.767). There was a greater reduction in VLDL-C with P-OM3 + FENO than with FENO monotherapy (-57.6 vs -47.6%, respectively; P=0.016). There was a greater reduction in RLP-C with P-OM3 + FENO than with FENO monotherapy (-72.0 vs -62.1%; P=0.029). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly reduced TGs compared to the end of the DB treatment period (-17.5%, P=0.003). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly increased LDL-C (+8.1%; P=0.001) compared to the group previously receiving P-OM3 + FENO (+0.4%). There was no significant change in non-HDL-C following the addition of P-OM3 to FENO. VLDL-C and RLP-C were significantly reduced by the addition of P-OM3 (-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				15.4%, P=0.030 and -25.8%, P=0.035, respectively). There was no significant difference in final lipid results for those who received P-OM3 + FENO for 16 weeks and those in which P-OM3 was added to FENO monotherapy during the OL phase of the study. In the pooled analysis of all patients enrolled in the eight week OL extension phase, the overall reductions of TGs and VLDL-C were -60.0 and -56.5%, respectively (P<0.001 for both). Non-HDLC and TC were also significantly reduced (P<0.001) over the 16 week treatment period in the pooled analysis. LDL-C increased 52.2% (P<0.001). There was no significant change in apo B at the end of the 16 week treatment study (P=0.544). The treatments were generally well tolerated and there was no significant difference in the safety profiles. The most adverse events were upper respiratory infection, nausea, diarrhea, constipation, gastroenteritis, dyspepsia, and headache.
Koh et al.[47] (2012) Fenofibrate 160 mg/day vs omega-3 fatty acids 2 g/day vs placebo	PC, PG, RCT, SB Patients with primary hypertriglyceridemia (>150 mg/dL)	N=50 2 months	Primary: Change in baseline lipid profile; change in baseline vasomotor function, hsCRP, and fibrinogen; change in baseline adiponectin, HbA_{1c}, and insulin resistance Secondary: Not reported	Primary: Placebo treatment significant reduced TG and TG:HDL-C, but increased LDL-C from baseline. Omega-3 fatty acids significantly reduced TG and TG:HDL-C from baseline. Fenofibrate significantly reduced T C, TG, apo B, TG:HDL-C, and non-HDL-C, and increased HDL-C and apo AI from baseline. Effects of fenofibrate on TC and T G were both significant compared to placebo (P<0.05). The magnitude of change in HDL-C, apo AI, TG:HDL-C, and non-HDL-C were significantly different when omega-3 fatty acids and fenofibrate therapy were compared, but both treatments resulted in comparable improvements in TG (P<0.05). Placebo did not significantly improve flow-mediated dilator response to hyperemia, but omega-3 fatty acids and fenofibrate significantly improved flow-mediated dilator response to hyperemia after two months when compared to baseline (P<0.001), and when compared to placebo (P<0.001). Brachial artery dilator responses to nitroglycerin were not significantly different between any of the therapies. Placebo and omega-3 fatty acids did not significantly change hsCRP and fibrinogen levels relative to baseline measurements. Fenofibrate significantly reduced

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hsCRP and fibrinogen levels after two months compared to baseline (P<0.001) or when compared to placebo (P<0.05). Omega-3 fatty acids did not significantly change insulin, plasma adiponectin levels, or insulin sensitivity compared to placebo. Compared omega-3 fatty acids, fenofibrate significantly decreased fasting insulin (P=0.023) and increased plasma adiponectin (P=0.002) and insulin sensitivity (P=0.015). Secondary: Not reported
Koh et al.[48] (2006) Fenofibrate 200 mg QD and candesartan 16 mg QD vs fenofibrate 200 mg QD vs candesartan 16 mg QD	DB, PC, RCT, XO Patients with hypertriglyceridemia (≥150 mg/dL) and hypertension (≥140/90 mm Hg)	N=46 6 months	Primary: BP, lipid profile, inflammatory markers, vasomotor function, plasma malondialdehyde, adiponectin, and insulin resistance Secondary: Not reported	Primary: Fenofibrate, combined therapy, or candesartan therapy significantly reduced BP. However, combined therapy significantly reduced BP more than fenofibrate or candesartan alone (P<0.001). When compared to candesartan, fenofibrate or combined therapy significantly improved the lipoprotein profile. Fenofibrate alone or combined therapy significantly lowered TC, TG, apo B, and non-HDL-C levels (P<0.001 for all) and increased HDL-C levels (P<0.001) when compared to baseline. These reductions were significantly greater than those observed with candesartan alone (P<0.001). However, there were no significant differences between fenofibrate alone and fenofibrate plus candesartan for these parameters (P value not significant). All three treatment arms significantly improved flow-mediated dilator response to hyperemia. Combined therapy significantly decreased plasma malondialdehyde (a biomarker for oxidative stress), hsCRP, and soluble CD40L levels relative to baseline measurements. Importantly, these parameters were changed to a greater extent with combined therapy when compared to monotherapy (P<0.001, P=0.002, P=0.050, and P=0.032, respectively). Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. However, the magnitudes of these increases were not significantly different among the three therapies (P=0.246 for adiponectin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				levels and P=0.153 for insulin sensitivity). Secondary: Not reported
Insua et al.[49] (2002) Gemfibrozil 900 mg daily vs fenofibrate 200 mg QD	DB, DD, RCT, XO Patients between the ages of 45 and 70 years with primary hyperlipo-proteinemia, Fredrickson phenotypes IIa and IIb	N=21 6 weeks	Primary: Cholesterol-lowering effectiveness Secondary: Not reported	Primary: Both drugs significantly reduced TC, calculated LDL-C, TG, apo B, and fibrinogen (P<0.01 for all calculations, except P<0.05 for fibrinogen with gemfibrozil therapy) and increased HDL-C (P<0.01). Neither drug affected Lp(a), whereas uric acid was reduced only by fenofibrate (P<0.01). The percentage decrease in TC and LDL-C was greater with fenofibrate compared to gemfibrozil (-22 vs -15%; P<0.02; and -27 vs -16%; P<0.02, respectively). In contrast, reductions in levels of TG (-54 vs -46.5%), apo B, and fibrinogen, as well as the increase in HDL-C (9% for both drugs), showed no significant difference between treatments. Separate analysis of patients with type IIb hyperlipoproteinemia showed essentially the same plasma lipid changes as for the overall group, but with greater modifications in TG and HDL-C concentrations. Secondary: Not reported
Corbelli et al.[50] (2002) Gemfibrozil (mean daily dose 1,200 mg) vs fenofibrate (mean daily dose of 201 mg)	RETRO Patients who were switched from gemfibrozil to fenofibrate, due to inadequate lipid response or adverse effects	N=92 23 months	Primary: Mean TC, TG, HDL-C, and non-HDL-C Secondary: Not reported	Primary: Compared to gemfibrozil, patients showed statistically significant improvements in mean TC, TG, HDL-C, and non-HDL (P<0.005). Specifically, more patients achieved a TG goal <200 mg/dL with fenofibrate (64%) compared to gemfibrozil (39%; P<0.0005). The study demonstrated that patients switched from gemfibrozil to fenofibrate due to an inadequate lipid response experienced significant improvements in lipid parameters for up to 18 months. Secondary: Not reported
Guyton et al.[51]	DB, MC, PC, RCT	N=173	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2000) Niacin ER (Niaspan®) titrated up to 1,000 mg at bedtime for 4 weeks, followed by 1,500 mg at bedtime for 4 weeks, followed by 2,000 mg at bedtime for 8 weeks vs gemfibrozil 600 mg BID	Patients 21 to 75 years of age with HDL-C ≤40 mg/dL, LDL-C ≤160 mg/dL or <130 mg/dL with atherosclerotic disease and TG ≤400 mg/dL	8 weeks	Effect on HDL-C Secondary: Change in other lipoproteins, adverse effects	Niacin 1,500 and 2,000 mg/day significantly increased HDL-C by 21 and 26%, respectively, compared to 13% with gemfibrozil (P<0.02). Secondary: Compared to gemfibrozil, niacin 1,500 and 2,000 mg/day significantly increased apo AI (9 and 11 vs 4%), reduced TC:HDL-C ratio (-17 and -22 vs -12%), reduced Lp(a) (-7 and -20 vs no change) and had no adverse effect on LDL-C (2 and 0 vs 9%; P<0.001 to P<0.02.). TG decreased by 40% with gemfibrozil compared to 16 and 29% with niacin 1,000 (P<0.001) and 2,000 mg/day (P<0.06). Effects on plasma fibrinogen levels were significantly favorable for niacin compared to gemfibrozil (-1 to -6% vs 5 to 9%, respectively; P<0.02). Flushing was significantly more frequent with niacin compared to gemfibrozil at every point (78 vs 10%; P values not reported). Flu syndrome occurred more frequently with niacin (P=0.006). Dyspepsia was more frequent with gemfibrozil (P=0.009).
Stalenhoef et al.[52] (2000) Omega-3-acid ethyl esters (Omacor*) 4 g/day vs gemfibrozil 1,200 mg/day	DB, DD, RCT Patients with primary hyper-triglyceridemia	N=28 12 weeks	Primary: Change in lipid profile, LDL-C subfraction profile Secondary: Not reported	Primary: Both omega-3-acid ethyl esters and gemfibrozil resulted in similar and significant decreases in serum TG, VLDL-TG and VLDL-C concentrations and increases in HDL-C and LDL-C (P=0.05 to P<0.001 from baseline and P=0.29 to P=1.00 between groups). Both therapies resulted in a more buoyant LDL-C subfraction profile (P=0.05 for omega-3-acid ethyl esters, P<0.01 for gemfibrozil and P=0.09 between groups in favor of gemfibrozil). Secondary: Not reported
van Dam et al.[53] (2001) Omega-3 acid ethyl esters (Omacor*) 4 g/day	RCT, DB Patients with hypertriglyceridemia (TG >400 mg/dL)	N=89 12 weeks	Primary: Percent change in TG Secondary: Percent change in	Primary: The mean percent change in TG was -28.9% with omega-3 acid ethyl esters and -51.2% with gemfibrozil (P=0.007). Secondary: The mean percent change in HDL-C and TC were +1.2 and -10.2%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs gemfibrozil 1,200 mg/day			TC, HDL-C, VLDL-C	respectively, with omega-3 acid ethyl esters and +27.9 and -13.0%, respectively, with gemfibrozil (P=0.012 and P=0.513, respectively). The mean percent change in VLDL-C was -11.8% with omega-3 acid ethyl esters and -19.4% with gemfibrozil (P=0.494).
Primary Prevention of Coronary Heart Disease Events				
Keech et al.[54] (2005) FIELD Fenofibrate 200 mg QD vs placebo	DB, PC, RCT Patients aged 50 to 75 years with type 2 diabetes mellitus	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI) Secondary: Total cardiovascular events which included the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularization; total mortality	Primary: Coronary events occurred in 5.9% of patients on placebo and 5.2% of patients on fenofibrate (HR, 0.89; 95% CI, 0.75 to 1.05; P=0.16). There was a 24% reduction in nonfatal MI with fenofibrate (HR, 0.76; 95% CI, 0.62 to 0.94; P=0.010). There was a nonsignificant increase in coronary heart disease mortality (HR, 1.19; 95% CI, 0.90 to 1.57; P=0.22). Secondary: Total cardiovascular disease events were significantly reduced from 13.9 to 12.5% with fenofibrate (HR, 0.89; 95% CI, 0.80 to 0.99; P=0.035). There was a 21% reduction in coronary revascularization with fenofibrate (HR, 0.79; 95% CI, 0.68 to 0.93; P=0.003). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (P=0.18).
Tonkin et al.[55] (2012) FIELD Fenofibrate 200 mg QD vs placebo	Subgroup analysis of FIELD comparing the effect of fenofibrate on cardiovascular disease between patients with prior cardiovascular disease and those without Patients aged 50 to	N=9,975 (n=2,131 with prior cardio-vascular disease and n=7,664 without prior cardio-vascular disease)	Primary: Lipids and the effect of fenofibrate treatment, compliance with trial medication and use of other drugs, unadjusted effect of treatment on outcomes, components of	Primary: There were small but significant differences between patients with and without prior cardiovascular disease in their pattern of lipid response to treatment. At 12 months after randomization, the effect of fenofibrate on increasing HDL-C and decreasing LDL-C and TG was greater in patients with no prior cardiovascular disease compared to those with prior cardiovascular disease (P<0.05 for all). At 24 months after randomization, difference in treatment effect between prior cardiovascular subgroups were observed for HDL-C (P=0.046) and TG (P=0.002). At trial end, differences were observed for LDL-C (P=0.01) and TG (P=0.006). Over the course of the trial, patients receiving placebo had a higher uptake

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	75 years with type 2 diabetes mellitus	5 years	total cardiovascular disease, adjusted analyses of treatment effect Secondary: Not reported	of lipid-lowering therapy (mainly statins) compared to those receiving fenofibrate (17 vs 8%). There was a higher uptake of statins among patients with prior cardiovascaular disease compared those without and a slightly higher uptake of other cardiovascular medications. Patients with prior cardiovascular disease discontinued fenofibrate more often than those without prior cardiovascular disease (14 vs 9%). The unadjusted effect of fenofibrate on future total cardiovascular disease events differed by prior cardiovascular disease status (interaction P=0.05). There was an independently significant reduction in the risk of a cardiovascular disease event (HR, 0.81; 95% CI, 0.70 to 0.94; P=0.004) in the group without prior cardiovascular disease, whereas in the prior cardiovascular disease group, there was no significant effect of treatment (HR, 1.02; 95% CI, 0.86 to 1.20; P=0.9). There was a significant difference in treatment effect between those with and those without prior cardiovascular disease for coronary events (interaction P=0.03) but not stroke (P=0.56) or revascularization (P=0.053). For coronary events, there was an independently significant reduction in the risk of an event (HR, 0.75; 95% CI, 0.59 to 0.94; P=0.01) in the group without prior cardiovascular disease, whereas in the prior cardiovascular disease group, there was no significant effect of treatment (HR, 1.08; 95% CI, 0.84 to 1.38; P=0.55). After the adjustment for uneven uptake of statins and other cardiovascular disease medications across treatment arms, the treatment-by-prior-cardiovascular disease interaction term remained significant (statins only; P=0.05 and statins plus other cardiovascular disease medications; P=0.04). However, after adjustment for baseline covariates, differences in treatment effects were no longer significant (P=0.06). Secondary: Not reported
Ting et al (abstract).[56] (2012) FIELD	Subgroup analysis of FIELD evaluating the effects of fenofibrate on cardiovascular and	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI),	Primary: The benefit of fenofibrate observed within the FIELD trial (HR, 0.89; 95% CI, 0.80 to 0.99; P=0.035), was not statistically different across eGFR groupings analyzed within this subgroup analysis (interaction P=0.2)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fenofibrate 200 mg QD vs placebo	ESRD events, according to eGFR Patients aged 50 to 75 years with type 2 diabetes mellitus		safety Secondary: Not reported	(eGFR 30 to 50 mL/min/1.73m^2: HR, 0.68; 95% CI, 0.47 to 0.97; P=0.035; eGFR ≥90 mL/min/1.73m^2: HR, 0.85; 95% CI, 0.70 to 1.02; P=0.08). ESRD rates were similar between treatment arms, without adverse safety signals of fenofibrate use in renal impairment. Secondary: Not reported
DAIS[57] (2001) Fenofibrate, micronized 200 mg QD vs placebo	PC, RCT Men and women with type 2 diabetes with good glycemic control, who had mild lipoprotein abnormalities typical of type 2 diabetes and at least one visible coronary lesion	N=418 3 years	Primary: Mean percentage stenosis, minimum coronary artery lumen diameter, mean segment diameter Secondary: Not reported	Primary: Plasma TC, HDL-C, LDL-C, and TG concentrations all changed significantly more from baseline in the fenofibrate group (N=207) compared to the placebo group (N=211). The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group (mean 2.11 vs 3.65; P=0.02), a significantly smaller decrease in minimum lumen diameter (-0.06 vs -0.10 mm; P=0.029), and an insignificant smaller decrease in mean segment diameter (-0.06 vs -0.08 mm; P=0.171). The trial was not powered to examine clinical end points. Secondary: Not reported
No authors listed.[58] ACCORD (2010) Fenofibrate 160 mg/day vs placebo All patients were receiving	DB, MC, PC, RCT Patients 40 to 79 years of age with type 2 diabetes and HbA_{1c} ≥7.5%, LDL-C 60 to 180 mg/dL, HDL-C <55 mg/dL for women or <50 mg/dL for men and TG <750 mg/dL if they were not receiving lipid	N=5,518 5 years	Primary: First occurrence of a major cardiovascular event (nonfatal MI, nonfatal stroke or death from cardiovascular causes) Secondary: Combination of the primary outcome	Primary: The annual rate of the primary outcome was 2.2% with fenofibrate and 2.4% with placebo (HR, 0.92; 95% CI, 0.79 to 1.08; P=0.32). Secondary: The annual rate of the primary outcome plus revascularization or hospitalization for CHF was 5.35% with fenofibrate and 5.64% with placebo (HR, 0.94; 95% CI, 0.85 to 1.05; P=0.30). The annual rate of major coronary disease events was 2.58% with fenofibrate and 2.79% with placebo (HR, 0.92; 95% CI, 0.79 to 1.07; P=0.26).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
simvastatin.	therapy or <400 mg/dL if they were		plus revascularization or hospitalization for CHF; a combination of a fatal coronary event, nonfatal MI or unstable angina; nonfatal MI; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; hospitalization or death due to heart failure	The annual rate of nonfatal MI was 1.32% with fenofibrate and 1.44% with placebo (HR, 0.91; 95% CI, 0.74 to 1.12; P=0.39). The annual rate of stroke was 0.38% with fenofibrate and 0.36% with placebo (HR, 1.05; 95% CI, 0.71 to 1.56; P=0.80). The annual rate of death from any cause was 1.47% with fenofibrate and 1.61% with placebo (HR, 0.91; 95% CI, 0.75 to 1.10; P=0.33). Rates for death from a cardiovascular cause were 0.72 and 0.83% (HR, 0.86; 95% CI, 0.66 to 1.12; P=0.26). The annual rate of fatal or nonfatal CHF was 0.90% with fenofibrate and 1.09% with placebo (HR, 0.82; 95% CI, 0.62 to 1.05; P=0.10).
Bonds et al.[59] (2012) ACCORD Fenofibrate 160 mg/day vs placebo All patients were receiving simvastatin.	Subgroup analysis of ACCORD, evaluating outcomes in patients with a fenofibrate-associated creatinine increase (increase in serum creatinine of ≥20% from baseline to month 4 in patients receiving fenofibrate) Patients 40 to 79 years of age with type 2 diabetes and HbA_{1c} ≥7.5%, LDL-C 60 to 180 mg/dL, HDL-C <55 mg/dL for women or <50	N=1,212 (patients who experienced a fenofibrate-associated creatinine increase) 5 years	Primary: Characteristics predicting creatinine elevation Secondary: Long-term renal and cardiovascular outcomes	Primary: Patients who were older, male, used an angiotensin converting enzyme-inhibitor at baseline, used a thiazolidinedione at four months post-randomization, had baseline cardiovascular disease, and had lower baseline serum creatinine and LDL-C were all more likely to meet the criteria for fenofibrate-associated creatinine increase). Secondary: No differences in study outcomes were seen by fenofibrate-associated creatinine increase; there was no increase in renal disease or cardiovascular outcome observed in patients demonstrating fenofibrate-associated creatinine increases.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	mg/dL for men and TG <750 mg/dL if they were not receiving lipid therapy or <400 mg/dL if they were			
Frick et al.[60] (1987) Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, RCT Asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive pretreatment measurements)	N=4,081 5 years	Primary: Risk of CHD measured by incidence of cardiac events Secondary: Total mortality	Primary: There were minimal changes in serum lipid levels in the placebo group. The cumulative rate of cardiac end points at five years was 27.3 per 1,000 in the gemfibrozil group and 41.4 per 1,000 in the placebo group, a reduction of 34% in the incidence of CAD (95% CI, 8.2 to 52.6; P<0.02; two-tailed test). The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. Secondary: There was no difference between the groups in the total death rate, nor did the treatment influence the cancer rates.
Frick et al.[61] (1993) Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, RCT Individuals who exhibited symptoms and signs of possible CHD during screening in the Helsinki Heart Study	N=311 5 years	Primary: Risk of CAD measured by incidence of cardiac events Secondary: Total mortality	Primary: The end point rate, consisting of fatal and nonfatal MI and cardiac death, did not differ significantly between the placebo and gemfibrozil groups. Since there were key prognostic factors missing (e.g., true prevalence of CHD, extent of coronary artery obstructions, degree of left ventricular dysfunction, and their distribution in the groups render the results less reliable), the data cannot be used to refute the thesis that treatment of dyslipidemia in manifest CHD is successful. Secondary: Total mortality did not differ significantly between the placebo and gemfibrozil groups.
Heinonen et al.[62] (1994) Helsinki Heart Study Gemfibrozil 600 mg BID	DB, MC Asymptomatic middle-aged men (40 to 55 years of age) with non-HDL-C greater than or equal to 200 mg/dL in 2	N=2,046 3.5 years	Primary: Definite fatal and nonfatal CHD events Secondary: Not reported	Primary: During the post-trial period the numbers of definite CHD events in both groups (54 vs 47; P value not significant) were smaller than expected without treatment, namely a reduction of around 40% for the original treatment groups. The mean incidence rates were in fact similar to that in the placebo group five years earlier. Cardiovascular mortality over the entire study period was similar but all-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	consecutive pretreatment measurements)			cause mortality was slightly higher among men of the original gemfibrozil group compared to the placebo group men (P=0.19). Secondary: Not reported
Huttunen et al.[63] (1994) Gemfibrozil 600 mg BID vs placebo	ES Asymptomatic adult patients with primary dyslipidemia (non-HDL-C ≥200 mg/dL in 2 consecutive pretreatment measurements)	N=4,081 8.5 years (follow-up)	Primary: Gastrointestinal symptoms, surgery, strokes, cancer incidence, morality by cause Secondary: Not reported	Primary: A first occurrence of a moderate to severe gastrointestinal side effect, mainly dyspepsia and abdominal pain, was reported by 20.1 and 15.1% of patients receiving gemfibrozil and placebo during the original five year trial (*P*<0.001). Side effects were reported at a consistently lower rate during the post-trial follow up than during the DB trial period. After switching from placebo to gemfibrozil, 4.6% of patients interrupted treatment as a result of adverse events (3.7% due to gastrointestinal symptoms). There was a nonsignificant excess of some illnesses and surgical procedures with gemfibrozil during the five year trial period. During the 3.5 year post trial follow-up, cholecystectomies and appendectomies continued to be more common with gemfibrozil. Strokes due to any cause were slightly less common with gemfibrozil. Ischemic strokes continued to occur less frequently in the original gemfibrozil groups, whereas hemorrhagic strokes were about equal post-trial. The cumulative incidences of malignancies and cancer cases by type during the 8.5 years of follow-up were similar, except basal cell skin carcinoma (16 vs 9; *P*=0.18). Over the 8.5 year follow up there were 101 deaths with gemfibrozil and 83 deaths with placebo. The distributions by causes of death did not differ significantly (*P*=0.12). The difference in cancer-specific deaths (30 vs 18) was mainly because of cancer deaths during the post-trial follow up (20 vs 7), while post-trial cardio- and cerebrovascular mortality was equal (25 vs 23, respectively). Deaths caused by cerebrovascular accidents were similar during the entire 8.5 year follow up (8 vs 6). There were fewer fatal cerebral infarctions (1 vs 5) and more fatal intracranial hemorrhages (7 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				1) with gemfibrozil. The excess mortality due to accidents or violence was reversed during the post-trial follow up, resulting in approximately equal numbers by the end of the trial. Total mortality with the two treatments remained almost equal during the trial period and the first year of the post-trial follow up; the excess mortality emerged towards the end (*P*=0.19). Secondary: Not reported
Robins et al.[64] (2001) VA-HIT Gemfibrozil 1,200 mg daily vs placebo	DB, MC, PC, RCT Men with a history of CHD who had low HDL-C levels and low LDL-C levels	N=2,531 7 years	Primary: Nonfatal MI or death from coronary causes Secondary: Not reported	Primary: Compared to placebo, gemfibrozil showed a 22% decreased risk of nonfatal MI or death due to CHD (17.3 vs 21.7%; P=0.006). Compared to placebo, gemfibrozil showed a 24% decreased risk for nonfatal MI, death due to CHD or confirmed stroke (20 vs 26%; P<0.001). A nonsignificant difference was seen in all-cause mortality with gemfibrozil compared to placebo (15.7 vs 17.4%; P=0.23). Concentrations of HDL-C were inversely related to CHD events. Multivariable Cox proportional hazards analysis showed that CHD events were reduced by 11% with gemfibrozil for every 5 mg/dL (0.13 mmol/L) increase in HDL-C (P=0.02). Events were reduced even further with gemfibrozil beyond that explained by increases in HDL-C values, particularly in the second through fourth quintiles of HDL-C values during treatment. During gemfibrozil treatment, only the increase in HDL-C significantly predicted a lower risk of CHD events; according to multivariable analyses, neither TG nor LDL-C levels at baseline or during the trial predicted CHD events. Secondary: Not reported
Rubins et al.[65] (1999)	DB, MC, PC, RCT Men <74 years of age	N=2,531 5.1 years	Primary: Combined incidence of	Primary: The combined primary endpoint occurred in 21.7 vs 17.3% of patients receiving placebo and gemfibrozil, which led to gemfibrozil being

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gemfibrozil 1,200 mg/day vs placebo	with CHD, HDL-C ≤40 mg/dL, LDL-C ≤140 mg/dL, TG ≤300 mg/dL and no serious coexisting conditions	(mean follow up)	nonfatal MI or death from CHD Secondary: Incidence of stroke, death from any cause, TIA, revascularization procedures, carotid endarterectomy and hospitalization for unstable angina or CHF	associated with a reduction of 22% (95% CI, 7 to 35; P=0.006). The effect was consistent for both components of the endpoint, but was only significant for a reduction in nonfatal MI (death from CHD, 22%; 95% CI, -2 to 41; P=0.07 and nonfatal MI, 23%; 95% CI, 4 to 38; P=0.02). The beneficial effect of gemfibrozil did not become apparent until about two years after randomization. Secondary: Gemfibrozil was not associated with a reduction in the incidence of stroke (6.0 vs 4.6%; RR reduction, 25%; 95% CI, -6 to 47; P=0.10). Gemfibrozil resulted in a RR reduction of 24% for the combined outcome of death from CHD, nonfatal MI or confirmed stroke (95% CI, 11 to 36; P<0.001). Gemfibrozil was associated with a significant reduction in the risk of TIA (RRR, 59%; 95% CI, 33 to 75; P<0.001). Gemfibrozil was associated with a significant reduction in the risk of carotid endarterectomy (RR reduction, 65%; 95% CI, 37 to 80; P<0.001). The rates of death from any case, coronary revascularization, hospitalization for unstable angina and cancer did not differ significantly between treatments.
Saha et al.[66] (2007) Fibrate therapy (bezafibrate*, clofibrate*, fenofibrate, gemfibrozil)	MA, SR (10 RCTs) Patients receiving fibrate therapy for the prevention of cardiovascular events (primary and secondary prevention)	N=36,489 Mean duration of follow up ≥1 year (32 months to 18 years)	Primary: All-cause mortality, cardiovascular and non-cardiovascular mortality, fatal and nonfatal MI and stroke Secondary: Incidence of cancer and cancer related mortality	Primary: On pooled MA, the use of fibrate therapy tended to increase all-cause mortality (pooled OR, 1.07; P=0.08) and significantly increased the odds of noncardiovascular mortality by about 16% (pooled OR, 1.16; P=0.004). Fibrate therapy had no significant effect on cardiovascular mortality, with a pooled OR of 0.98 (P=0.68). The use of fibrate therapy did not affect the occurrence of fatal MI (pooled OR, 0.96; P=0.76), but significantly reduced the odds of nonfatal MI by about 22% (pooled OR, 0.78; P<0.00001). Fibrate therapy also had no significant effect on stroke, with a pooled OR of 0.96 (P=0.56). Secondary: The use of fibrates was not associated with an increase in the odds of developing cancer (pooled OR, 1.00; P=0.98) or cancer related mortality (pooled odds ratio, 1.11; P=0.17).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Subgroup analyses revealed that the risk of all-cause mortality did not significantly differ among the various fibrates used. Noncardiovascular mortality was significantly higher with the use of clofibrate on pooled analysis of data from two primary prevention trials (pooled OR, 1.35; 95% CI, 1.13 to 1.62; P=0.001). The odds of cardiovascular mortality tended to be lower with gemfibrozil with a pooled OR of 0.77 (P=0.05), whereas neither bezafibrate nor fenofibrate had any significant effect on mortality. The odds of nonfatal MI were lower with gemfibrozil (pooled OR, 0.72; P=0.001) than with bezafibrate (pooled OR, 0.78; P=0.02) or fenofibrate (pooled OR, 0.77; P=0.01). No significant differences were observed among the different fibrates with regard to their effects on fatal MI, stroke, cancer or cancer related mortality.
Jun et al.[67] (2010) Fibrate therapy (bezafibrate*, clofibrate*, etofibrate*, fenofibrate and gemfibrozil) vs placebo	MA, SR (18 PRO, RCTs) Demographics not reported	N=45,058 Duration varied	Primary: Major cardiovascular events, coronary events, stroke, heart failure, coronary revascularization, all-cause mortality, cardiovascular death, nonvascular death, sudden death, new onset albuminuria, drug related adverse events Secondary: Not reported	Primary: Data for coronary events were available from 16 trials, including 44,667 patients in whom 4,552 coronary events were recorded. Overall, fibrate therapy reduced the risk of coronary events by 13% (RR, 0.87; 95% CI, 0.81 to 0.93; P<0.0001). Ten trials, including 42,131 patients, reported 2,485 nonfatal coronary outcomes with fibrate therapy, reducing the risk by 19% (RR, 0.81; 95% CI, 0.75 to 0.89); P<0.0001). For the 1,740 coronary deaths recorded in 13 trials no effect was noted (RR, 0.93; 95% CI, 0.85 to 1.02; P=0.116). Effects on coronary revascularization were reported in four trials, including 15,834 patients whom 1,737 events were reported, with fibrate therapy significantly reducing the risk by 12% (RR, 0.88; 95% CI, 0.78 to 0.98; P=0.025). A cumulative MA of all trials reporting coronary outcomes demonstrated consistent benefit from fibrate therapy on the risk of coronary events. Eight trials, including 27,021 patients, reported 1,391 stroke events, with no evidence that fibrate therapy protected against stroke risk (RR, 1.03;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				95% CI, 0.91 to 1.16; P=0.687). Three trials, including 8,581 patients, reported 584 heart failure events, with no evidence that fibrate therapy protected against heart failure risk (RR, 0.94; 95% CI, 0.65 to 1.37; P=0.759). Sixteen trials, including 44,813 patients, reported 3,880 deaths, with six trials reporting separate data for vascular death (22,066 patients with 1,545 reported vascular deaths) and five trials providing separate data for sudden death (12,277 patients reported 596 sudden deaths). No effect of fibrate therapy on the risk of all-cause mortality (RR, 1.00; 95% CI, 0.93 to 1.08; P=0.918), vascular mortality (RR, 0.97; 95% CI, 0.88 to 1.07; P=0.587) or sudden death (RR, 0.89; 95% CI, 0.74 to 1.06; P=0.190) was noted. An increased risk of nonvascular mortality was noted; however, this finding did not reach significance (RR, 1.10; 95% CI, 0.995 to 1.21; P=0.063). Three trials reported on the progression of albuminuria, including 15,731 patients and 3,859 events, with fibrate therapy reducing the risk by 14% (RR, 0.86; 95% CI, 0.75 to 0.98; P=0.028). Four trials reported data for total adverse events (17,413 patients reporting 225 events), demonstrating no significant increase in the risk of serious drug-related adverse events (RR, 22%; 95% CI, -9 to 61; P=0.19). Fibrate therapy did not significantly increase the risk of rhabdomyolysis (RR, 35%; 95% CI, -59 to 439; P=0.42), muscle abnormalities (RR, 0%; 95% CI, -1 to 2; P=0.69), gastrointestinal disorders (RR, 8%; 95% CI, -1 to 18; P=0.08) and gallbladder disease (RR, 19%; 95% CI, -11 to 60; P=0.24). Fibrate therapy was associated with an increase in creatinine (RR increase, 99%; 95% CI, 46 to 270; P<0.0001). Secondary: Not reported

*Agent not available within the United States.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, QD=once daily, SR=sustained-release
Study abbreviations: AC=active comparator, DB=double-blind, DD=double dummy, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open-label, PA=parallel arm, PC=placebo controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective study, SB=single-blind, SR=systematic review, XO=crossover
Miscellaneous abbreviations: apo=apolipoprotein, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BP=blood pressure, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, CRP=C-reactive protein, eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease,

HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HOMA-IR=Homeostasis Model of Assessment-Insulin Resistance, HR=hazard ratio, hsCRP=high sensitivity C-reactive protein, ICAM-1=intercellular adhesion molecule-1, IDL-C=intermediate-density lipoprotein-cholesterol , LDL-C=low-density lipoprotein cholesterol, Lp(a)=Lipoprotein(a), MI=myocardial infarction, MMP9=matrix metallopeptidase 9, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, RLP=remnant like particle cholesterol, RR=relative risk, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TRL=triglyceride rich lipoproteins, VCAM-1=vascular cell adhesion molecule-1, VLDL-C=very low-density lipoprotein cholesterol

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Fibric Acid Derivatives

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Fenofibrate	capsule, tablet	Lofibra®*, Lipofen®	$$$$	$$
Fenofibrate, micronized	capsule	Antara®, Lofibra®*	$$$$	$
Fenofibrate, nanocrystallized	tablet	Tricor®*, Triglide®	$$$$	N/A
Fenofibric acid	delayed-release capsule, tablet	Fibricor®*, Trilipix®	$$$$	$$$
Gemfibrozil	tablet	Lopid®*	$$$$	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The fibric acid derivatives are approved for the treatment of hypertriglyceridemia, primary hypercholesterolemia, and mixed dyslipidemia.[1-9] They decrease triglycerides by 20 to 50% and increase high-density lipoprotein cholesterol (HDL-C) by 10 to 35%. They can also lower low-density lipoprotein cholesterol (LDL-C) by 5 to 20%; however, LDL-C may increase in patients with hypertriglyceridemia.[10] Fenofibrate (micronized and non-micronized formulations), fenofibric acid, and gemfibrozil are available in a generic formulation.

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease (CHD) or CHD equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant, niacin, or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy. The fibric acid derivatives are considered an option in patients who are unable to take a statin, but are typically reserved for the treatment of hypertriglyceridemia, to reduce the risk of pancreatitis, or for an isolated low HDL-C. They can also be considered an option for the treatment of patients with CHD who have low levels of LDL-C and atherogenic dyslipidemia, or in combination with a statin in patients who have elevated LDL-C and atherogenic dyslipidemia. Guidelines do not give preference to one fibric acid derivative over another.[1,13-18]

Clinical trials have demonstrated that the fibric acid derivatives can effectively lower triglycerides and increase HDL-C, as well as positively impact other lipid/lipoprotein parameters. Complementary lipid effects were also observed in clinical trials when fibric acid derivatives were coadministered with ezetimibe and statins.[20-53] In the FIELD trial, fenofibrate was associated with a nonsignificant reduction in CHD events in patients with type 2 diabetes, as well as a non-significant increase in total and CHD. However, fenofibric was associated with a significant reduction in total cardiovascular disease events and revascularization compared to placebo.[54] Furthermore, in the ACCORD trial, there was no difference between combination therapy with fenofibrate and simvastatin and monotherapy with simvastatin in the annual rate of first occurrence of major cardiovascular events in high-risk type 2 diabetics.[58] In the Helsinki Heart Study, gemfibrozil was associated with a significant reduction in CHD in asymptomatic men with dyslipidemia compared to placebo.[60] In a secondary prevention component of the Helsinki Heart Study, there was no difference observed between gemfibrozil and placebo in the incidence of fatal and nonfatal myocardial infarction and cardiac death.[61] Overall, because of chemical, pharmacological, and clinical similarities between the fibric acid derivatives, the findings from these studies may apply to all of the agents in this class.[1-9,11,12]

There is insufficient evidence to support that one brand fibric acid derivative is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand fibric acid derivatives within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand fibric acid derivative is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of HMG-CoA Reductase Inhibitors
AHFS Class 240608
February 13, 2013

I. Overview

The antilipemic agents are categorized into five different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins) and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Adminsitration-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

The statins include single entity agents (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin), as well as fixed-dose combination products (amlodipine-atorvastatin, ezetimibe-simvastatin, niacin-lovastatin, and niacin-simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors. Statins also decrease the release of lipoproteins from the liver.[1-13] The statins are by far the most effective class of drugs to lower LDL-C. Depending on the agent selected, the statins can decrease LDL-C by 18 to 60% when used as monotherapy.[14,15] The effects on LDL-C are dose-dependent and log-linear. There is an additional 6% reduction in LDL-C with each doubling of the dose. The statins also decrease triglycerides by 7 to 30% and increase high-density lipoprotein cholesterol (HDL-C) by 5 to 15%.[14]

Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.[11] The exact mechanism by which niacin alters lipids is not completely understood. It may inhibit the mobilization of free fatty acids from adipose tissue, decrease the delivery of free fatty acids to the liver, decrease triglyceride synthesis, alter the hepatic production of apolipoprotein B, and increase HDL-C by reducing its catabolism.[1,10] Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension, chronic stable angina and vasospastic angina, as well as to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease.[3]

The HMG-CoA reductase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The lipid-lowering effects of the statins are noted in Table 2. Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and amlodipine-atorvastatin are available in a generic formulation. This class was last reviewed in August 2010.

Table 1. HMG-CoA Reductase Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Atorvastatin	tablet	Lipitor®*	atorvastatin
Fluvastatin	capsule, extended-release tablet	Lescol®*, Lescol XL®	fluvastatin
Lovastatin	extended-release tablet, tablet	Altoprev®, Mevacor®*	lovastatin
Pitavastatin	tablet	Livalo®	none
Pravastatin	tablet	Pravachol®*	pravastatin
Rosuvastatin	tablet	Crestor®	none
Simvastatin	tablet	Zocor®*	simvastatin
Combination Products			
Amlodipine and atorvastatin	tablet	Caduet®*	amlodipine/atorvastatin
Ezetimibe and simvastatin	tablet	Vytorin®	none

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Niacin and lovastatin	extended-release tablet	Advicor®	none
Niacin and simvastatin	extended-release tablet	Simcor®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.

Table 2. Lipid-lowering Effects of the HMG-CoA Reductase Inhibitors*[1-13,16]

Generic Name(s)	Total Cholesterol ↓ (%)	LDL-C ↓ (%)	Triglycerides ↓ (%)	HDL-C ↑ (%)
Single Entity Agents				
Atorvastatin	25 to 58	27 to 60	17 to 53	5 to 14
Fluvastatin	16 to 25	22 to 38	12 to 25	2 to 11
Lovastatin	16 to 34	21 to 42	10 to 27	5 to 12
Pitavastatin	22 to 35	31 to 45	13 to 22	1 to 8
Pravastatin	16 to 33	22 to 41	10 to 24	1 to 14
Rosuvastatin	24 to 46	28 to 63	10 to 43	3 to 22
Simvastatin	19 to 52	26 to 51	8 to 41	7 to 16
Combination Products				
Amlodipine and atorvastatin	25 to 58	27 to 60	17 to 53	5 to 14
Ezetimibe and simvastatin	31 to 43	45 to 60	23 to 31	6 to 10
Niacin and lovastatin	Not reported	30 to 42	32 to 44	20 to 30
Niacin and simvastatin†	2 to 11	5 to 14	22 to 38	8 to 19

*Includes studies in the prescribing information. Data are mean changes from baseline; data are pooled from different studies and may not be directly comparable.
†Patients were receiving simvastatin 20 to 40 mg at baseline.
HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the HMG-CoA reductase inhibitors are summarized in Table 3.

Table 3. Treatment Guidelines Using the HMG-CoA Reductase Inhibitors

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[17] (2004)**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with

Clinical Guideline	Recommendation
	high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report[14] (2002)**	<u>General recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Statins</u> • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.

Clinical Guideline	Recommendation
	Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. Omega-3 fatty acids • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Heart	Lipid management

Clinical Guideline	Recommendation
Association/American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update[18] (2011)**	• Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable. • For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults[15] (2011)**	Clinical highlights • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures. • Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established coronary artery disease, non-cardiac atherosclerosis, or coronary artery disease equivalent. Ongoing drug therapy • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30%

Clinical Guideline	Recommendation
	reduction in CHD events. <u>Monotherapy</u> • Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and important adverse effect of statin therapy. • Specific statin and dose should be selected based on cost and amount of lipid-lowering required. • If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available. • Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia. • Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc). • Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin. • Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate). • Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease. • The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin. • The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown. • Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most

Clinical Guideline	Recommendation

	potent with a statin.
	• Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after.
	
	Combination therapy
	• It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe.
	  ○ A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy.
	  ○ No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events.
	  ○ The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy compared to statin monotherapy on clinical vascular endpoints.
	• Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy.
	• Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit.
	• There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins.
	• No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy.
	
	Lifestyle modifications
	• Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss.
	• Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range.
	• A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended.
	• Vitamin E supplementation should not be used.
	• Light to moderate consumption of alcohol may lower CHD rates.
	• Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).

American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association[19] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in

Clinical Guideline	Recommendation
	patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice[20] (2012)**	Drugs • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy to decrease LDL-C. • Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. • Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. • Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. Drug combinations • Patients with dyslipidemia, particularly those with established CVD, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
National Institute for Health and Clinical Excellence: **Lipid Modification[21] (2010)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of cardiovascular disease for adults who have a ≥20% 10 year risk of developing cardiovascular disease.

Clinical Guideline	Recommendation
	• Treatment for the primary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of cardiovascular disease. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of cardiovascular disease. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of cardiovascular disease. • Statin therapy is recommended for adults with clinical evidence of cardiovascular disease. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dL) or LDL-C <2 mmol/L (<77 mg/dL) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with cardiovascular disease who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[22] (2011)**	• Risk factor control for all patients with transient ischemic attack (TIA) or ischemic stroke: • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD. • For patients with atherosclerotic ischemic stroke or TIA without known CHD, it is reasonable to target a reduction of ≥50% in LDL-C or a target LDL-C level <70 mg/dL to obtain maximal benefit. • Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to the National Cholesterol Education Program III guidelines (i.e., lifestyle modification, dietary guidelines, medication recommendations). • Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the HMG-CoA reductase inhibitors are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the HMG-CoA Reductase Inhibitors[1-12]

Indications	Single Entity Agents							Combination Products			
	Atorva-statin	Fluva-statin	Lova-statin	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodipine and atorva-statin*	Ezetimibe and simva-statin	Niacin and lova-statin†	Niacin and simva-statin‡
Hypertriglyceridemia											
Reduce elevated triglycerides (TG) in patients with hypertriglyceridemia							✔				✔
Treatment of adult patients with hypertriglyceridemia						✔					
Treatment of adult patients with very high serum TG levels who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them										✔ (niacin)	
Treatment of patients with elevated TG levels	✔				✔			✔ (atorva-statin)			
Primary Hypercholesterolemia and Mixed Dyslipidemia											
Reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B), and TG and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia and mixed dyslipidemia	✔	✔	✔ § (ER)	✔	✔	✔	✔	✔ (atorva-statin)	✔	✔ ‖ (niacin)	✔
Reduce TC, LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 (lovastatin only) or 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular risk	✔ ¶	✔ #	✔ ** (IR)		✔ ††	✔ **	✔ **	✔ ¶ (atorva-statin)			

Indications	Single Entity Agents							Combination Products			
	Atorva-statin	**Fluva-statin**	**Lova-statin**	**Pitava-statin**	**Prava-statin**	**Rosuva-statin**	**Simva-statin**	**Amlodipine and atorva-statin***	**Ezetimibe and simva-statin**	**Niacin and lova-statin†**	**Niacin and simva-statin‡**
factors are present in the pediatric patient											
Reduce elevated TG and very LDL-C in patients with primary dysbetalipoproteinemia							✔				
Reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔						✔	✔ (atorva-statin)	✔		
Reduce TC, LDL-C, and apo B in adult patients with homozygous familial hypercholesterolemia as adjunctive therapy to other lipid-lowering treatments or alone if such treatments are not available						✔					
Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia			✔ §							✔ § (lova-statin)	
Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	✔				✔	✔		✔ (atorva-statin)			
Prevention of Cardiovascular Disease											
Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels						✔					
Reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes, and without clinically evidence coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension	✔							✔ (atorva-statin)			
Reduce the risk of myocardial infarction, stroke, and for revascularization procedures and angina in adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family	✔							✔ (atorva-statin)			

Indications	Single Entity Agents							Combination Products			
	Atorva-statin	Fluva-statin	Lova-statin	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodipine and atorva-statin*	Ezetimibe and simva-statin	Niacin and lova-statin†	Niacin and simva-statin‡
history of early coronary heart disease											
Reduce the risk of myocardial infarction, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident coronary heart disease					✔						
Reduce the risk of myocardial infarction, unstable angina, and coronary revascularization procedures in patients without symptomatic cardiovascular disease, average to moderately elevated TC and LDL-C, and below average HDL-C			✔							✔ (lova-statin)	
Reduce the risk of non-fatal myocardial infarction, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evidence coronary heart disease	✔							✔ (atorva-statin)			
Reduce the risk of recurrent non-fatal myocardial infarction in patients with a history of myocardial infarction and hypercholesterolemia										✔ (niacin)	
Reduce the risk of stroke, myocardial infarction, and arterial revascularization procedures in patients without clinically evidence coronary heart disease but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease						✔					
Reduce the risk of total mortality by reducing coronary death, myocardial infarction, undergoing myocardial revascularization					✔						

Indications	Single Entity Agents							Combination Products			
	Atorva-statin	Fluva-statin	Lova-statin	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodipine and atorva-statin*	Ezetimibe and simva-statin	Niacin and lova-statin†	Niacin and simva-statin‡
procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evidence coronary heart disease											
Reduce the risk of total mortality by reducing coronary heart disease deaths, non-fatal myocardial infarction and stroke, and need for coronary and non-coronary revascularization procedures in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease							✔				
Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evidence coronary heart disease		✔									
Slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower TC and LDL-C to target levels			✔							✔ (lova-statin)	
Other											
Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease by angiography and without heart failure or an ejection fraction <40%								✔ (amlodipine)			
Symptomatic treatment of chronic stable angina								✔ (amlodipine)			
Treatment of confirmed or suspected vasospastic angina								✔ (amlodipine)			
Treatment of hypertension								✔ (amlodipine)			

*Indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.
†Indicated for use when treatment with both niacin and lovastatin is appropriate.
‡Indicated for use when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
║When the response to an appropriate diet has been inadequate.
¶In boys and postmenarchal girls 10 to 17 years of age.
#In adolescent boys and adolescents girls who are at least one year post-menarche, 10 to 16 years of age.
**In adolescents boys and girls, who are at least one year post-menarche, 10 to 17 years of age.
††In children and adolescent patients ages eight years of age and older.
ER=extended-release, IR=immediate-release.

IV. Pharmacokinetics

The pharmacokinetic parameters of the HMG-CoA reductase inhibitors are listed in Table 5. All statins undergo extensive first-pass metabolism, resulting in relatively low bioavailability following oral administration. However, the hepatic HMG-CoA inhibition occurs as a result of the high liver concentrations during first-pass metabolism. Thus, their therapeutic effect is not lessened by this high first-pass extraction.[13,16]

Table 5. Pharmacokinetic Parameters of the HMG-CoA Reductase Inhibitors[16]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Atorvastatin	14	98	Liver (significant; % not reported)	Renal (1 to 2) Bile (primary; % not reported)	7 to 14
Fluvastatin	20 to 30	98	Liver (% not reported)	Renal (5) Bile (95) Feces (95)	<3
Lovastatin	5	>95	Liver (extensive; % not reported)	Renal (10) Feces (83)	Not reported
Pitavastatin	51*	99	Liver (extensive; % not reported)	Renal (15) Bile (extensive; % not reported) Feces (79)	11 to 12
Pravastatin	17	43 to 55	Liver (extensive; % not reported)	Renal (20) Feces (71)	2.6 to 3.2
Rosuvastatin	20	88	Liver (minimal; % not reported)	Renal (10) Feces (90)	19
Simvastatin	5	95	Liver (extensive; % not reported)	Renal (13) Feces (60)	Not reported
Combination Products					
Amlodipine and atorvastatin	AM: 64 to 90 AT: 14	AM: 93 AT: 98	AM: Liver (extensive; % not reported) AT: (significant; % not reported)	AM: Renal (70) AT: Renal (1 to 2) Bile (primary; % not reported)	AM: 30 to 60 AT: 7 to 14
Ezetimibe and simvastatin	E: not reported S: 5	E: >90 S: 95	E: Liver (% not reported) Small intestine (extensive; % not reported) S: Liver (extensive; % not reported)	E: Renal (11) Feces (78) S: Renal (13) Feces (60)	E: 19 to 30 S: not reported
Niacin and lovastatin	N: 60 to 76 L: 5	N: not reported L: >95	N: Liver (rapid; % not reported) L: Liver (extensive; % not reported)	N: Renal (60 to 76) L: Renal (10) Feces (83)	N: not reported L: not reported
Niacin and simvastatin	N: 60 to 76 S: 5	N: not reported S: 95	N: Liver (rapid; % not reported) S: Liver (extensive; % not reported)	N: Renal (60 to 76) S: Renal (13) Feces (60)	N: not reported S: not reported

*Oral solution.
AM=amlodipine, AT=atorvastatin, E=ezetimibe, L=lovastatin, N=niacin, S=simvastatin

V. Drug Interactions

Significant drug interactions with the HMG-CoA reductase inhibitors are listed in Table 6.

Table 6. Significant Drug Interactions with the HMG-CoA Reductase Inhibitors[13]

Generic Name(s)	Significance Level	Interaction	Mechanism
Amlodipine	1	Simvastatin	The mechanism of interaction is unknown. Simvastatin plasma concentrations may be elevated, increasing the risk of toxicity.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Amiodarone	Inhibition of cytochrome P450 isoenzymes by amiodarone may decrease the metabolic elimination of HMG-CoA reductase inhibitors. The pharmacologic effects of HMG-CoA reductase inhibitors may be increased by amiodarone. Elevated plasma concentrations with toxicity characterized by muscle injury may occur.
HMG-CoA reductase inhibitors (fluvastatin, lovastatin, rosuvastatin, simvastatin)	1	Anticoagulants	The hypoprothrombinemic effects of anticoagulants may be increased HMG-CoA reductase inhibitors. Hematuria, epistaxis and rectal bleeding may occur. The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)	1	Azole antifungals	Azole antifungals may inhibit first-pass hepatic metabolism of HMG-CoA reductase inhibitors, increasing plasma levels and adverse reactions of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	1	Cyclosporine	Cyclosporine may decrease the elimination of HMG-CoA reductase inhibitors by inhibiting their metabolism. Toxic effects of HMG-CoA reductase inhibitors including liver enzyme elevation, myopathy, and rhabdomyolysis may be increased by cyclosporine.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Delavirdine	Delavirdine inhibits HMG-CoA reductase metabolism, increasing HMG-CoA reductase inhibitor plasma concentrations and increasing the risk of severe myopathy or rhabdomyolysis.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Diltiazem	The inhibition of cytochrome P450 (CYP) 3A4 isoenzymes by diltiazem may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by co-administration of diltiazem. The risk of myopathy and rhabdomyolysis may be increased.
HMG-CoA reductase inhibitors (atorvastatin,	1	Efavirenz	Induction of CYP3A4 isoenzymes by efavirenz may increase the metabolic elimination of HMG-CoA reductase

Generic Name(s)	Significance Level	Interaction	Mechanism
lovastatin, pravastatin, simvastatin)			inhibitors. Efavirenz may decrease plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin)	1	Fibric acid derivatives	Coadministration of fibric acid derivatives with HMG-CoA reductase inhibitors may result in myopathy or rhabdomyolysis.
HMG-CoA reductase inhibitors (all)	1	Hepatitis C virus (HCV) protease inhibitors	HCV protease inhibitors may inhibit the metabolism of HMG-CoA reductase inhibitors, increasing plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors (rosuvastatin)	1	Protease inhibitors	Inhibition of CYP3A4 isoenzymes by human immunodefiency virus (HIV) protease inhibitors may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Pharmacologic and toxic effects of HMG-CoA reductase inhibitors may be increased by HIV protease inhibitors.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Macrolides and related antibiotics	Inhibition of CYP3A4 isoenzymes by macrolides and ketolides may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Macrolides and ketolides may increase pharmacologic effects of HMG-CoA reductase inhibitors. Elevated plasma concentrations with toxicity characterized by liver enzyme elevation and myopathy may occur.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Mifepristone	Mifepristone may inhibit the metabolism of HMG-CoA reductase inhibitors, increasing HMG-CoA reductase inhibitor plasma concentrations and pharmacologic effects.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	1	Nefazodone	Inhibition of CYP3A4 isoenzymes by nefazodone may decrease the metabolic elimination of HMG-CoA reductase inhibitors. The risk of myopathy and rhabdomyolysis may be increased when HMG-CoA reductase inhibitors and nefazodone are coadministered.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, pravastatin, simvastatin)	1	Non-nucleoside reverse transcriptase inhibitors (NNRT inhibitors)	Inhibition of CYP3A4 isoenzymes by NNRT inhibitors may decrease the metabolic elimination of HMG-CoA reductase inhibitors. NNRT inhibitors may increase plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors.
HMG-CoA reductase inhibitors	1	Ranolazine	Ranolazine inhibits the metabolism of HMG-CoA reductase inhibitors,

Generic Name(s)	Significance Level	Interaction	Mechanism
(atorvastatin, lovastatin, simvastatin)			increasing HMG-CoA reductase inhibitor plasma concentrations and increasing the risk of adverse events.
Ezetimibe	2	Cyclosporine	When cyclosporine and ezetimibe are co-administered, exposure to both drugs may be increased potentially increasing the pharmacologic effects and adverse reactions. The mechanism of this interaction is unknown.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Carbamazepine	Induction of CYP3A4 metabolism by carbamazepine may cause increased metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be decreased by carbamazepine.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Imatinib	Inhibition of CYP3A4 isoenzymes by imatinib may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by imatinib.
HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin)	2	Rifamycins	Induction of pre-hepatic and hepatic CYP3A4-mediated metabolism by rifamycins may increase the metabolic elimination of HMG-CoA reductase inhibitors. Pharmacologic effects of HMG-CoA reductase inhibitors may be decreased by rifamycins and impaired cholesterol-lowering efficacy may result.
HMG-CoA reductase inhibitors (atorvastatin, lovastatin, simvastatin)	2	Verapamil	Inhibition of CYP3A4 isoenzymes by verapamil may decrease the metabolic elimination of HMG-CoA reductase inhibitors. Plasma concentrations and pharmacologic effects of HMG-CoA reductase inhibitors may be increased by verapamil. Toxicity, characterized by muscle injury, may occur.

Significance Level 1 = major severity.
Significance Level 2 = moderate severity.

VI. Adverse Drug Events

The most common adverse drug events reported with the HMG-CoA reductase inhibitors are listed in Table 7. These agents are generally well tolerated with only mild side effects, such as abdominal pain, constipation, flatulence and headache. Myopathy has also been reported with the HMG-CoA reductase inhibitors, which can progress to rhabdomyolysis and acute renal failure. Risk factors for developing rhabdomyolysis include age >65 years, hypothyroidism, and poor renal function. Increases in hepatic transaminases greater than three times the upper limit of normal have also been reported with the HMG-CoA reductase inhibitors.[1-13,16]

Table 7. Adverse Drug Events (%) Reported with the HMG-CoA Reductase Inhibitors[1-13,16]

Adverse Event	Single Entity Agents							Combination Products			
	Atorva-statin	**Fluva-statin (IR/ER)**	**Lova-Statin (IR/ER)**	**Pitava-statin**	**Prava-statin**	**Rosuva-statin**	**Simva-statin**	**Amlodipine and atorvastatin**	**Ezetimibe and simvastatin**	**Niacin and lovastatin**	**Niacin and simvastatin**
Cardiovascular											
Angina pectoris	<2	-	-	-	3.1	-	-	-	-	-	-
Arrhythmia	<2	-	-	-	0.1 to 2.6	-	-	<2/✓	-	-	-
Bradycardia	-	-	-	-	-	-	-	-/✓	-	-	-
Chest pain	≥2	-	0.5 to 1.0	-	-	-	-	≥2.0/✓	-	-	-
Hypertension	<2	-	-	-	-	-	-	-	-	-	-
Hypotension	-	-	-		-	-	-	-/✓	-	-	-
Migraine	<2	-	-	-	-	-	-	-	-	-	-
Palpitation	<2	-	-	-	-	-	-	<2/0.7 to 4.5	-	-	-
Peripheral ischemia	-	-	-		-	-	-	✓/-	-	-	-
Postural hypotension	<2	-	-	-	-	-	-	<2/✓	-	-	-
Syncope	<2	-	-	-	-	-	-	<2/✓	-	-	-
Tachycardia	-	-	-	-	-	-	-	-/✓	-	-	-
Vasodilatation	<2	-	-	-	-	-	-	-/✓	-	-	-
Central Nervous System/Neurological											
Abnormal dreams	<2	-	-	-	-	-	-	<2/✓	-	-	-
Amnesia	<2	-	-	-	-	-	-	-	-	-	-
Anxiety	-	✓	✓	-	1	-	✓	-/✓	-	-	-
Chills	-	✓	✓	-	✓	-	✓	-	-	-	-
Cranial nerve dysfunction	-	✓	✓	-	✓	-	✓	-	-	-	-
Depersonalization	-	-	-	-	-	-	-	-/✓	-	-	-
Depression	<2	✓	✓	-	1	-	✓	<2/✓	-	-	-
Dizziness	≥2	✓	0.5 to 1.2/2.0	-	1.0 to 2.2	≤4	✓	≥2.0/1.1 to 3.4	-	-	-
Emotional lability	<2	-	-	-	-	-	-	-	-	-	-
Facial paralysis/paresis	<2	✓	-	-	✓	-	✓	-	-	-	-
Fever	<2	✓	-	-	<1	-	✓	-	-	-	-
Flushing	-	✓	✓	-	<1	-	✓	-/0.7 to 4.5	-	71	59
Headache	2.5 to 16.7	8.9/4.7	✓	✓	1.7 to 1.9	3.1 to 8.5	3.5	2.5 to 16.7/7.3	5.8	-	4.5
Hyperkinesia	<2	-	-	-	-	-	-	-	-	-	-
Hypertonia	<2	-	-	-	-	-	-	-	-	-	-
Hypesthesia	<2	-	-	-	-	-	-	-/✓	-	-	-
Impairment of extraocular	-	✓	-	-	✓	-	-	-	-	9	-

Adverse Event	Single Entity Agents							Combination Products			
	Atorva-statin	Fluva-statin (IR/ER)	Lova-Statin (IR/ER)	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin	Niacin and lovastatin	Niacin and simvastatin
movement											
Incoordination	<2	-	-	-	-	-	-	-	-	-	-
Insomnia	≥2	2.7/0.8	0.5 to 1.0	-	1	-	✔	≥2/✔	-	-	-
Libido decreased	<2	✔	✔	-	<1	-	✔	-	-	-	-
Memory loss	-	✔	✔	-	<1	✔	✔	-	-	-	-
Neck rigidity	<2	-	-	-	-	-	-	-	-	-	-
Nervousness	-	-	-	-	-	-	-	-/✔	-	-	-
Paresthesia	<2	✔	0.5 to 1.0/-	-	<1	-	✔	<2/✔	-	-	-
Peripheral nerve palsy	-	✔	✔	-	<1	-	✔	-	-	-	-
Peripheral neuropathy	<2	✔	✔	-	<1	-	✔	-	-	-	-
Psychiatric disturbances	-	✔	✔	-	<1	-	✔	<2/✔	-	-	-
Somnolence	<2	-	-	-	-	-	-	<2.0/1.3 to 1.6	-	-	-
Tremor	-	✔	✔	-	<1	-	✔	-/✔	-	-	-
Vertigo	-	✔	✔	-	<1	-	✔	-/✔	-	-	-
Dermatological											
Acne	<2	-		-	-	-	-	-	-	-	-
Alopecia	<2	✔	0.5 to 1.0/-	-	<1	-	✔	-	-	-	-
Contact dermatitis	<2	-	-	-	-	-	-	-	-	-	-
Dry skin	<2	✔	✔	-	<1	-	✔	-	-	-	-
Eczema	<2	-	-	-	-	-	0.8	-	-	-	-
Erythema multiforme	<2	✔	✔	-	✔	-	✔	<2/✔	-	-	-
Pruritis	<2	✔	0.5 to 1.0/-	-	<1	<2	0.5	<2/✔	-	7	3.2
Rash	1.1 to 3.9	✔	0.8 to 1.3/-	-	1.3 to 2.1	<2	0.6	<2/✔	-	5	-
Rash erythematous	-	-	-	-	-	-	-	-/✔	-	-	-
Rash maculopapular	-	-	-	-	-	-	-	-/✔	-	-	-
Seborrhea	<2	-	-	-	-	-	-	-	-	-	-
Skin ulcer	<2	-	✔	-	-	-	-	-	-	-	-
Stevens-Johnson syndrome	✔	✔	-	-	✔	-	✔	-	-	-	-
Sweating	<2	-	-	-	-	-	-	<2/✔	-	-	-
Toxic epidermal necrolysis	✔	✔	✔	-	✔	-	✔	-	-	-	-
Urticaria	<2	✔	✔	-	-	<2	-	-	-	-	-
Endocrine and Metabolic											
Gout	<2	-	-	-	-	-	-	-	-	-	-
Hyperglycemia	<2	✔	-	-	-	-	-	<2/✔	-	4	-
Hypoglycemia	<2	-	-	-	-	-	-	-	-	-	-
Peripheral edema	≥2	-	-	-	-	-	-	<2/✔	-	-	-
Thirst	-	-	-	-	-	-	-	-/✔	-	-	-
Weight decrease	-	-	-	-	-	-	-	-/✔	-	-	-
Weight gain	<2	-	-	-	-	-	-	<2/✔	-	-	-
Gastrointestinal											
Abdominal pain	0.0 to 3.8	4.9/3.7	2.0 to 2.5/-	-	2.0 to 2.4	≤2.4	0.9 to 3.2	0 to 3.8/1.6	-	4	-

Adverse Event	Single Entity Agents							Combination Products			
	Atorva-statin	Fluva-statin (IR/ER)	Lova-Statin (IR/ER)	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin	Niacin and lovastatin	Niacin and simvastatin
Acid regurgitation	-	-	0.5 to 1.0/-	-	-	-	-	-	-	-	-
Anorexia	<2	✔	✔	-	-	-	✔	0 to 3.8/1.6	-	-	-
Biliary pain	<2	-	-	-	-	-	-	-	-	-	-
Cheilitis	<2	-	-	-	-	-	-	-	-	-	-
Cholestatic jaundice	<2	✔	✔	-	✔	✔	✔	-	-	-	-
Cirrhosis	-	✔	✔	-	✔	-	✔	-	-	-	-
Colitis	<2	-	-	-	-	-	-	-	-	-	-
Constipation	0 to 2.5	-	2.0 to 3.5/-	1.5 to 3.6	1.2 to 2.4	2.1 to 4.7	2.3	0 to 2.5/✔	-	-	-
Decreased appetite	-	-	-	-	<1	-	-	-	-	-	-
Diarrhea	0 to 5.3	4.9/3.3	2.2 to 2.6 to 3.0	1.5 to 2.6	2	-	0.5 to 1.9	0 to 5.3/✔	2.8	6	3
Dry mouth	<2	-	0.5 to 1.0/-	-	-	-	-	<2/✔	-	-	-
Duodenal ulcer	<2	-	-	-	-	-	-	-	-	-	-
Dyspepsia/heartburn	1.3 to 2.8	7.9/3.5	1.0 to 1.6/-	-	2.0 to 3.5	-	0.6 to 1.1	1.3 to 2.8/✔	-	3	-
Dysphagia	<2	-	-	-	-	-	-	<2/✔	-	-	-
Enteritis	<2	-	-	-	-	-	-	-	-	-	-
Eructation	<2	-	-	-	-	-	-	-	-	-	-
Esophagitis	<2	-	-	-	-	-	-	-	-	-	-
Flatulence	1.1 to 2.8	2.6/1.4	3.7 to 4.5	-	1.2 to 2.7	-	0.9 to 1.9	1.1 to 2.8/✔	-	-	-
Fulminant hepatic necrosis	-	✔	✔	-	✔	-	✔	-	-	-	-
Gastritis	<2	-	-	-	-	-	-	-	-	-	-
Gastroenteritis	<2	-	-	-	-	-	-	-	-	-	-
Gingival hyperplasia	-	-	-	-	-		-	-/✔	-	-	-
Glossitis	<2	-	-	-	-	-	-	-	-	-	-
Gum hemorrhage	<2	-	-	-	-	-	-	-	-	-	-
Hepatitis	<2	✔	✔	-	✔	✔	✔	-	-	-	-
Hepatoma	-	✔	✔	-	✔	-	✔	-	-	-	-
Increased appetite	<2	-	-	-	-	-	-	-	-	-	-
Melena	<2	-	-	-	-	-	-	-	-	-	-
Mouth ulceration	<2	-	-	-	-	-	-	-	-	-	-
Nausea	≥2	3.2/2.5	-	-	1.6 to 2.9	0 to 6.3	0.4 to 1.3	≥2.0/2.9	-	7	3.2
Pancreatitis	<2	✔	✔	-	✔	<2	✔	<2/✔	-	-	-
Rectal hemorrhage	<2	-	-	-	-	-	-	-	-	-	-
Stomach ulcer	<2	-	-	-	-	-	-	-	-	-	-
Stomatitis	<2	-	-	-	-	-	-	-	-	-	-
Tenesmus	<2	-	-	-	-	-	-	-	-	-	-
Ulcerative stomatitis	<2	-	-	-	-	-	-	-	-	-	-
Vomiting	<2	✔	0.5 to 1.0/-	-	1.6 to 2.9	-	✔	<2/✔	-	3	-
Genitourinary											
Abnormal ejaculation	<2	-	-	-	-	-	-	-	-	-	-
Albuminuria	≥2	-	-	-	-	-	-	-	-	-	-
Breast enlargement	<2	-	-	-	-	-	-	-	-	-	-

Adverse Event	Single Entity Agents							Combination Products			
	Atorva-statin	**Fluva-statin (IR/ER)**	**Lova-Statin (IR/ER)**	**Pitava-statin**	**Prava-statin**	**Rosuva-statin**	**Simva-statin**	**Amlodipine and atorvastatin**	**Ezetimibe and simvastatin**	**Niacin and lovastatin**	**Niacin and simvastatin**
Cystitis	<2	-	-	-	-	-	-	-	-	-	-
Dysuria	<2	-	-	-	<1	-	-	-	-	-	-
Epididymitis	<2	-	-	-	-	-	-	-	-	-	-
Erectile dysfunction	-	✔	✔	-	<1	-	✔	-	-	-	-
Fibrocystic breast	<2	-	-	-	-	-	-	-	-	-	-
Gynecomastia	-	✔	✔	-	✔	-	✔	-	-	-	-
Hematuria	≥2	-	-	-	-	-	-	-	-	-	-
Impotence	<2	-	-	-	-	-	-	-	-	-	-
Kidney calculus	<2	-	-	-	-	-	-	-	-	-	-
Metrorrhagia	<2	-	-	-	-	-	-	-	-	-	-
Nephritis	<2	-	-	-	-	-	-	-	-	-	-
Nocturia	<2	-	-	-	<1	-	-	<2/✔	-	-	-
Urinary abnormality	-	-	-	-	0.7 to 1.0	-	-	-/✔	-	-	-
Urinary frequency	<2	-	-	-	<1	-	-	<2/✔	-	-	-
Urinary incontinence	<2	-	-	-	-	-	-	-	-	-	-
Urinary retention	<2	-	-	-	-	-	-	-	-	-	-
Urinary tract infection	≥2	1.6/2.7	-/2	-	-	-	-	-	-	-	-
Urinary urgency	<2	-	-	-	1	-	-	-	-	-	-
Uterine hemorrhage	<2	-	-	-	-	-	-	-	-	-	-
Vaginal hemorrhage	<2	-	-	-	-	-	-	-	-	-	-
Hematologic											
Anemia	<2	-	-	-	-	-	-	-	-	-	-
Ecchymosis	<2	-	-	-	-	-	-	-	-	-	-
Eosinophilia	-	✔	✔	-	✔	-	✔	-	-	-	-
Hemolytic anemia	-	✔	✔	-	✔	-	✔	-	-	-	-
Leukopenia	-	✔	✔	-	✔	-	-	-/✔	-	-	-
Lymphadenopathy	<2	-	-	-	-	-	-	-	-	-	-
Petechia	<2	-	-	-	-	-	-	-	-	-	-
Prolongation of prothrombin time	-	-	-	-	-	-	-	-	-	-	✔
Purpura	-	✔	✔	-	✔	-	✔	-/✔	-	-	-
Thrombocytopenia	<2	✔	✔	-		-	✔	2/✔	-	-	✔
Vasculitis	-	✔	✔	-	✔	-	✔	-/✔	-	-	-
Laboratory Test Abnormalities											
γ-glutamyl transpeptidase increase	-	-	-	-	-	-	-	-	-	-	✔
Abnormal thyroid function tests	-	-	-	-	-	-	-	-	-	-	✔
Bilirubin elevation	-	✔	✔	✔	-	✔	✔	-	-	-	✔
Creatine phosphokinase increased	<2	-	-	✔	-	2.6	✔	-	-	-	✔
Eosinophil sedimentation rate increase	-	✔	✔	-	✔	-	✔	-	-	-	-
Fasting glucose increase	-	-	-	-	-	-	-	-	-	-	✔
Hematuria	-	-	-	-	-	✔	-	-	-	-	-
Lactate dehydrogenase decrease	-	-	-	-	-	-	-	-	-	-	✔
Liver enzyme abnormalities	-	✔	✔	✔	✔	2.2	✔	-	0.4 to 3.7	-	✔

Adverse Event	Single Entity Agents							Combination Products			
	Atorva-statin	Fluva-statin (IR/ER)	Lova-Statin (IR/ER)	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin	Niacin and lovastatin	Niacin and simvastatin
Phosphorus decrease	-	-	-	-	-	-	-	-	-	-	✔
Positive antinuclear antibody	-	✔	✔	-	✔	-	✔	-	-	-	-
Proteinuria	-	-	-	-	-	✔	-	-	-	-	-
Thyroid level abnormality	-	✔	✔	-	✔	✔	✔	-	-	-	-
Uric acid increase	-	-	-	-	-	-	-	-	-	-	✔
Musculoskeletal											
Arthralgia	0 to 5.1	-/3.2	0.5 to 1.5/5.0	✔	6	10.1	✔	0 to 5.1/✔	-	-	-
Arthritis	≥2	2.1/1.3	0.5 to 6.0/5.0	-	✔	-	✔	-/✔	-	-	-
Back pain	0 to 3.8	-	-/5	1.4 to 3.9	-	-	-	0 to 3.8/✔	0.4	5	3.2
Bursitis	<2	-	-	-	-	-	-	-	-	-	-
Dermatomyositis	-	-	-	-	✔	-	-	-	-	-	-
Leg cramps	<2	-	0.5 to 1.0/-	-	-	-	-	-	-	-	-
Leg pain	-	-	-	-	-	-	-	-	-	-	-
Localized pain	-	-	-	-	1.4	-	-	-	-	-	-
Muscle cramps	-	✔	0.6 to 1.1/-	-	2	-	✔	-/✔	-	-	-
Myalgia	0 to 5.6	5.0/3.8	1.8 to 3.0/3.0	1.9 to 3.1	0.6 to 1.4	1.9 to 12.7	1.2	0 to 5.6/✔	0.6 to 3.6	3	-
Myopathy	-	✔	-	-	✔	-	✔	-	-	-	-
Myositis	<2	-	-	-	-	-	-	-	-	-	-
Myasthenia	<2	-	-	-	<1	-	-	-	-	-	-
Pain in extremity	-	-	-	0.6 to 2.3	-	-	-	-	2.3	-	-
Polymyalgia rheumatica	-	✔	✔	-	✔	-	✔	-	-	-	-
Rhabdomyolysis	✔	✔	✔	-	✔	-	✔	-	-	-	-
Shoulder pain	-	-	0.5 to 1.0/-	-	-	-	-	-	-	-	-
Tendinous contracture	<2	-	-	-	-	-	-	-	-	-	-
Tenosynovitis	<2	-	-	-	-	-	-	-	-	-	-
Respiratory											
Asthma	<2	-	-	-	-	-	-	-	-	-	-
Bronchitis	≥2	1.2/2.6	-	-	-	-	-	-	-	-	-
Cough	-	-	-	-	0.1 to 1.0	-	-	-	-	-	-
Dyspnea	<2	✔	✔	-	1.6	-	✔	<2/✔	-	-	-
Epistaxis	<2	-	-	-	-	-	-	<2/✔	-	-	-
Pharyngitis	0 to 2.5	-	-	-	-	-	-	-	-	-	-
Pneumonia	<2	-	-	-	-	-	-	-	-	-	-
Rhinitis	≥2	-	-	-	0.1	-	-	-	-	-	-
Sinusitis	0 to 6.4	2.6/3.5	-/4	-	-	-	-	-	-	-	-
Upper respiratory infection	-	-	-	-	1.3	-	2.1	-	3.6	-	-
Other											
Abnormal vision	-	-	-	-	-	-	-	-/✔	-	-	-
Accidental injury	0 to 4.2	5.1/4.2	-/6	-	-	-	-	0 to 2.8/✔	-	-	-
Allergic reaction	0 to 2.8	2.3/1.0	-	-	<1	-	-	-	-	-	-
Amblyopia	<2	-	-	-	-	-	-	-	-	-	-
Anaphylaxis	✔	✔	✔	-	✔	-	✔	-	-	-	-
Angioedema	-	✔	✔	-	✔	<2	✔	-/✔	-	-	-

Adverse Event	Single Entity Agents							Combination Products			
	Atorva-statin	Fluva-statin (IR/ER)	Lova-Statin (IR/ER)	Pitava-statin	Prava-statin	Rosuva-statin	Simva-statin	Amlodipine and atorvastatin	Ezetimibe and simvastatin	Niacin and lovastatin	Niacin and simvastatin
Angioneurotic edema	✓	-	-	-	-	-	-	-	-	-	-
Asthenia	0 to 3.8	✓	1.2 to 2.0/3.0	-	✓	0.9 to 4.7	1.6	0 to 3.8/✓	-	5	-
Blurred vision	-	-	0.9 to 1.2/-	-	-	-	-	-	-	-	-
Cataracts	-	✓	✓	-	-	-	0.5	-	-	-	-
Conjunctivitis	-	-	-	-	-	-	-	-/✓	-	-	-
Deafness	<2	-	-	-	-	-	-	-	-	-	-
Diplopia	-	-	-	-	-	-	-	-/✓	-	-	-
Dry eyes	<2	-	-	-	-	-	-	-	-	-	-
Eye hemorrhage	<2	-	-	-	-	-	-	-	-	-	-
Eye irritation	-	-	0.5 to 1.0/-	-	-	-	-	-	-	-	-
Eye pain	-	-	-	-	-	-	-	-/✓	-	-	-
Facial/general edema	<2	-	-	-	<1	-	-	-	-	-	-
Fatigue	✓	2.7/1.6	-	-	1.9 to 3.4	-	-	✓/4.5	-	-	-
Flu syndrome	0 to 3.2	5.1/7.1	-/5	-	-	-	-	-	-	6	-
Glaucoma	<2	-	-/11	-	-	-	-	-	-	-	-
Hot flashes	-	-	-	-	-	-	-	-/✓	-	-	-
Infection	2.8 to 10.3	-	-	-	-	-	-	-	-	20	-
Influenza	-	-	-	✓	-	-	-	-	2.3	-	-
Lupus erythematosus-like syndrome	-	✓	✓	-	✓	-	✓	-	-	-	-
Malaise	<2	✓	✓	-	✓	-	✓	-	-	-	-
Nasopharyngitis	-	-	-	✓	-	-	-	-	-	-	-
Ophthalmoplegia	-	✓	✓	-	-	-	✓	-	-	-	-
Pain	-	-	-/3	-	-	-	-	-	-	-	-
Parosmia	<2	-	-	-	-	-	-	-	-	-	-
Photosensitivity reaction	<2	✓	-	-	✓	-	-	-	-	8	-
Refraction disorder	<2	-	-	-	-	-	-	-	-	-	-
Rigors	-	-	-	-	-	-	-	-/✓	-	-	-
Sexual dysfunction	-	-	-	-	-	-	-	-	-	-	-
Taste disturbance	<2	✓	-	-	✓	-	-	-/✓	-	-	-
Tinnitus	<2	-	-	-	-	-	-	<2/✓	-	-	-
Visual disturbances	-	-	✓	-	✓	-	-	-	-	-	-

✓ Percent not specified.
- Event not reported.
ER=extended-release, IR=immediate-release

VII. Dosing and Administration

The usual dosing regimens for the HMG-CoA reductase inhibitors are listed in Table 8. All statins are dosed once daily with the exception of maximum doses of lovastatin and fluvastatin immediate-release products, which should be divided into twice daily dosing. Atorvastatin, rosuvastatin and fluvastatin extended-release formulation are the only statins that may be administered at any time in the day. The other statins should be administered in the evening or at bedtime to target the time of maximum cholesterol synthesis.[1-12]

Table 8. Usual Dosing Regimens for the HMG-CoA Reductase Inhibitors[1-12]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Atorvastatin	Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 10 to 20 mg once daily; maintenance, 10 to 80 mg once daily	Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Tablet: initial, 10 mg/day; maximum, 20 mg/day Safety and efficacy in children <10 years of age have not been established.	Tablet: 10 mg 20 mg 40 mg 80 mg
Fluvastatin	Prevention of cardiovascular disease: Capsule, extended-release tablet: 20 to 80 mg/day Primary hypercholesterolemia and mixed dyslipidemia: Capsule: initial, 40 mg once daily or 40 mg twice daily Extended-release tablet: initial, 80 mg once daily	Heterozygous familial hypercholesterolemia in children 10 to 16 years of age: Capsule: initial, 20 mg once daily; maximum, 40 mg twice daily Extended-release tablet: maximum, 80 mg once daily Safety and efficacy in children <9 years of age have not been established.	Capsule: 20 mg 40 mg Extended-release tablet: 80 mg
Lovastatin	Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia: Extended-release tablet: 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day administered in a single or two divided doses; maximum, 80 mg/day	Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Tablet: 10 to 40 mg/day; maximum, 40 mg/day Safety and efficacy in children have not been established (extended-release tablet). Safety and efficacy in pre-pubertal patients or children <10 years of age have not been established (tablet).	Extended-release tablet: 20 mg 40 mg 60 mg Tablet: 20 mg 40 mg
Pitavastatin	Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 2 mg once daily; maintenance, 1 to 4 mg once daily; maximum, 4 mg/day	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 4 mg
Pravastatin	Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily	Heterozygous familial hypercholesterolemia in children >8 to 13 years of age: Tablet: initial, 20 mg once daily	Tablet: 10 mg 20 mg 40 mg 80 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		Heterozygous familial hypercholesterolemia in children 14 to 18 years of age: Tablet: initial, 40 mg once daily Safety and efficacy in children <8 years of age have not been established.	
Rosuvastatin	Hypertriglyceridemia /Prevention of cardiovascular disease /Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 10 to 20 mg once daily; maintenance, 5 to 40 mg once daily	Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Tablet: maintenance, 5 to 20 mg/day; maximum, 20 mg/day Safety and efficacy in pre-pubertal patients or children <10 years of age have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg
Simvastatin	Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 10 to 40 mg once daily; 5 to 40 mg/day	Heterozygous familial hypercholesterolemia in children 10 to 17 years of age: Tablet: initial, 10 mg once daily; maintenance, 10 to 40 mg/day; maximum, 40 mg/day Safety and efficacy in pre-pubertal patients or children <10 years of age have not been established.	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg
Combination Products			
Amlodipine and atorvastatin	Hypertension/Coronary artery disease (amlodipine): Tablet: initial, 5 mg once daily; maximum, 10 mg once daily Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed dyslipidemia (atorvastatin): Tablet: initial, 10 to 20 mg once daily; maintenance, 10 to 80 mg once daily	Safety and efficacy in children have not been established.	Tablet: 2.5-10 mg 2.5-20 mg 2.5-40 mg 5-10 mg 5-20 mg 5-40 mg 5-80 mg 10-10 mg 10-20 mg 10-40 mg 10-80 mg
Ezetimibe and simvastatin	Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 10-10 or 10-20 mg once daily; maintenance, 10-10 to 10-40 mg/day	Safety and efficacy in children have not been established.	Tablet: 10-10 mg 10-20 mg 10-40 mg 10-80 mg
Niacin and lovastatin	Hypertriglyceridemia/Prevention of cardiovascular disease/Primary hypercholesterolemia and mixed	Safety and efficacy in children have not been established.	Tablet: 500-20 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	dyslipidemia: Initial, 500-20 mg once daily in patients not currently receiving niacin; maintenance, dose should be individualized; maximum, >2,000-40 mg/day (not recommended)		750-20 mg 1,000-20 mg 1,000-40 mg
Niacin and simvastatin	Hypertriglyceridemia/Primary hypercholesterolemia and mixed dyslipidemia: Tablet: initial, 500-20 mg once daily in patients naïve to or switching from immediate-release niacin or 2,000-40 mg once daily in patients already receiving extended-release niacin; maintenance, 1,000-20 to 2,000 to 40 mg once daily; maximum, <2,000-40 mg/day (not recommended)	Safety and efficacy in children have not been established.	Tablet: 500-20 mg 500-40 mg 750-20 mg 1,000-20 mg 1,000-40 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the HMG-CoA reductase inhibitors are summarized in Table 9.

Table 9. Comparative Clinical Trials with the HMG-CoA Reductase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Single-entity Agents				
Familial Hypercholesterolemia (Single-Entity Agents)				
Rodenburg et al.[23] (2007) Pravastatin 20 mg (children <14 years of age) or pravastatin 40 mg (children ≥14 years of age)	FU Children diagnosed with FH, between 8 and 18 years of age, on a fat-restricted diet ≥3 months, with LDL-C ≥4.0 mmol/L and triglyceride levels <4.0 mmol/L on 2 different occasions, using adequate contraception, not on any treatment for hypercholesterolemia, including plant sterol or stanol products	N=214 2 years (mean duration of total treatment with a statin was 4.5 years)	Primary: Percentage change in TC, LDL-C, TG, HDL-C, predictors of smaller carotid IMT, and safety Secondary: Not reported	Primary: Statin therapy was associated with a 22.5% reduction in TC from baseline. Statin therapy was associated with a 29.2% reduction in LDL-C from baseline. Statin therapy was associated with a 3.1% increase in HDL-C from baseline. Statin therapy was associated with a 1.9% reduction in TG from baseline. The study found several independent predictors of smaller carotid IMT:IMT at statin initiation (P<0.001), age at statin initiation (P=0.016), male sex (P<0.001), and the duration of statin therapy (P<0.001). Secondary: Not reported
Avis et al.[24] (2010) PLUTO Rosuvastatin 5, 10 or 20 mg/day for 12 weeks	DB, MC, PC, RCT Children 10 to 17 years of age with a heFH by documentation of	N=177 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Changes from	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to placebo (38, 45 and 50 vs 1%; P<0.001 for all). Secondary: Compared to placebo, significant reductions with rosuvastatin were achieved for TC (P<0.001 for all) and apo B (P<0.001), but not for TG (P=0.8, P=0.1

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo All patients were randomized after a 6-week diet lead in period. After 12 weeks, patients entered a 40 week, OL, dose-titration phase. Patients originally randomized to placebo and those with LDL-C <100 mg/dL on their assigned rosuvastatin dose began the OL phase on rosuvastatin 5 mg/day. All others continued their rosuvastatin dose from the DB phase.	a genetic defect or by predefined clinical criteria, Tanner stage ≥11, with female patients being ≥1 year post menarche and fasting LDL-C ≥190 or >160 mg/dL if there was a family history of premature cardiovascular disease or if the patient had ≥2 other risk factors for cardiovascular disease		baseline in lipoproteins, proportion of patients achieving LDL-C goal (<110 mg/dL), safety	and P=0.1). HDL-C (P=0.4, P=0.2 and P=0.5) and apo AI (P=0.7, P=0.3 and P=0.6) were not significantly different from placebo. No patient receiving placebo achieved the LDL-C goal compared to 12, 41 and 41% of patients receiving rosuvastatin 5, 10 and 20 mg during the DB phase. In the OL phase, the goal was achieved by 40% of patients. A LDL-C goal of <130 mg/dL was achieved by 68% of patients in the OL phase. At the end of the OL phase, 26 patients were receiving rosuvastatin 5 mg, 25 patients were receiving 10 mg and 122 patients were receiving 20 mg. During the DB phase, the overall frequencies of adverse events were 50, 64, 55 and 54% (P value not reported). The most commonly reported adverse events included nasopharyngitis, influenza, myalgia and nausea. One serious adverse event of blurred vision occurred with placebo and one patient receiving rosuvastatin 20 mg had a vesicular rash during the OL phase. There was no hepatic, skeletal muscle or renal adverse events reported.
Avis et al.[25] (2007) Standard statin	MA (6 RCTs) Patients <18 years of age with heFH	N=798 Up to 2 years	Primary: Percentage change in TC, LDL-C, TG,	Primary: Statin therapy was associated with a 23% reduction in TC compared to placebo (95% CI, 19 to 27; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
therapy (pravastatin, fluvastatin, lovastatin, rosuvastatin, simvastatin, atorvastatin) vs placebo			HDL-C, apo B and apo AI; difference in absolute changes in IMT; safety Secondary: Not reported	Statin therapy was associated with a 30% reduction in LDL-C compared to placebo (95% CI, 24 to 36; P value not reported). Statin therapy was associated with a 3.6% increase in HDL-C compared to placebo (95% CI, 1.33 to 5.94; P value not reported). Statin therapy was associated with a 25% reduction in apo B compared to placebo (95% CI, 19 to 31; P value not reported). Statin therapy was associated with a 2.4% reduction in apo AI compared to placebo (95% CI, 0.41 to 4.45; P value not reported). Statin therapy was associated with a significant carotid IMT regression compared to placebo (P=0.02). Statin therapy was not associated with a significant risk of adverse events compared to placebo (RR, 0.99; 95% CI, 0.79 to 1.25). Statin therapy was not associated with a significant risk of AST (RR, 0.98; 95% CI, 0.23 to 4.26), ALT (RR, 2.03; 95% CI, 0.24 to 16.95) or CK elevation (RR, 1.38; 95% CI, 0.18 to 10.82) compared to placebo. Secondary: Not reported
Shafiq et al.[26] (2007) Statins (lovastatin, pravastatin, simvastatin, atorvastatin vs placebo	MA (6 trials) DB, RCTs comparing statins with placebo in pediatric and adolescent patients with FH	N=798 12 to 104 weeks	Primary Percent change in LDL-C, TC, TG, HDL-C Secondary: Not reported	Primary Statin therapy was associated with a significant reduction in LDL-C compared to placebo. Statin therapy was associated with a significant reduction in TC compared to placebo. Statin therapy was associated with a significant reduction in TG compared to placebo. Statin therapy was associated with a significant increase in HDL-C compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported
Marais et al.[27] (2008) Rosuvastatin 80 mg QD for 6 weeks vs atorvastatin 80 mg QD for 6 weeks All patients were randomized following a 18 week OL titration phase during which patients received rosuvastatin 20 mg QD for 6 weeks, titrated up to 40 mg/day for 6 weeks, titrated up to 80 mg/day for another 6 weeks, all after a 4 week dietary lead in period.	DB, RCT, XO Patients >10 years of age, weighing ≥32 kg with hoFH, fasting LDL-C >500 mg/dL, TG <600 mg/dL and either xanthomata before 10 years of age or both parents with FH	N=44 30 weeks (includes the 18 week OL titration phase)	Primary Percent change in LDL-C from baseline to week 18 Secondary Response rate; percent change in TC, apo B, TG and HDL-C	Primary Rosuvastatin 20 to 80 mg achieved a significant reduction in LDL-C from baseline after 18 weeks of therapy (21.4%; P<0.0001). Patients without a portacaval shunt and those not receiving plasmapheresis who received rosuvastatin 20 to 80 mg experienced a 15% reduction in LDL-C from baseline after 18 weeks of therapy (P value not reported). Secondary: Rosuvastatin was associated with an overall 72% response rate (≥15% reduction in baseline LDL-C) (P value not reported). Rosuvastatin 20 to 80 mg was associated with a significant reduction in TC and apo B from baseline after 18 weeks of therapy (20%; P<0.0001). Rosuvastatin 20 to 80 mg was associated with a nonsignificant increase in TG and HDL-C from baseline after 18 weeks of therapy (3.3 and 3.1%, respectively; P>0.05). At week 24, rosuvastatin and atorvastatin did not differ in the magnitude of LDL-C reduction from baseline (19.1 vs 18.0%; P=0.67). At week 24, there was no significant difference between treatments in reductions from baseline TC (17.6 vs 17.9%; P=0.91), TG (6.3 vs 13.9%; P=0.21) or apo B (11.4 vs 11.7%; P=0.90). The only significant difference between the two treatments was in the change from baseline in apo AI. While patients receiving rosuvastatin experienced an increase, atorvastatin-treated patients exhibited a reduction in apo AI (P=0.001).
Arca et al.[28] (2007) Atorvastatin 10 mg/day, titrated	OL, RCT Patients 30 to 75 years of age with diagnosis of	N=56 24 weeks	Primary: Change in TC, LDL-C, HDL-C, TG, apo A and endothelin-	Primary: Atorvastatin was associated with a significant 9% reduction in TC compared to fenofibrate (95% CI, 3.0 to 15.1; P=0.004). Atorvastatin was associated with a significant 17% reduction in LDL-C

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
up to 80 mg/day vs fenofibrate 200 mg/day	familial combined hyperlipidemia with TC and/or TG levels ≥90th Italian population percentiles, and/or hyper-apobeta-lipoproteinemia		1 Secondary: Not reported	compared to fenofibrate (95% CI, 8.0 to 26.1; P<0.001). Fenofibrate was associated with a significant 15.5% reduction in TG compared to atorvastatin (95% CI, 3.35 to 27.70; P=0.013). Fenofibrate was associated with a significant 14.2% increase in HDL-C compared to atorvastatin (95% CI, 3.8 to 24.6%; P=0.008). Fenofibrate was associated with a significant 5.2 and 22.0% increase in apo AI and apo AII compared to atorvastatin (P=0.044 and P<0.001, respectively). Fenofibrate was associated with a significant 16.7% reduction in endothelin-1 from baseline (P<0.05). Atorvastatin was not associated with a significant change in endothelin-1 (P value not reported). Secondary: Not reported
Gagné et al.[29] (2002) Statin 40 mg for up to 14 weeks, followed by the addition of ezetimibe 10 mg QD for another 12 weeks, administered as separate entities vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily and addition	DB, MC, RCT Patients ≥12 years old (or with body weight ≥40 kg) with hoFH, LDL-C ≥100 mg/dL and TG ≤350 mg/dL (if on atorvastatin or simvastatin 40 mg/day)	N=50 26 weeks	Primary: Percent change in LDL-C from baseline to the end of treatment period Secondary: Percent change from baseline in total cholesterol, TG, HDL-C, the ratios of LDL-C:HDL-C and TC:HDL-C, non–HDL-C, apo B, apo AI, and CRP	Primary: LDL-C was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (20.7 vs 6.7%; P=0.007). Secondary: TC was reduced more by the addition of ezetimibe 10 mg to the statin than by doubling the dose of statin (18.7 vs 5.3%; P<0.01). There was no statistically significant difference in any of the other secondary outcome measures between the two groups (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
of ezetimibe 10 mg QD daily for another 12 weeks, administered as separate vs statin 40 mg for up to 14 weeks, followed by titration to 80 mg daily Statins used in the study included simvastatin and atorvastatin.				
Hypercholesterolemia (Single Entity Agents)				
Koshiyama et al.[30] (2008) KISHIMEN Pitavastatin 1 to 2 mg/day	MC, OL, PRO Patients with TC ≥220 mg/dL and TG <400 mg/dL	N=178 12 months	Primary: Changes from baseline in LDL-C, HDL-C, remnant-like particle cholesterol, TG and hsCRP Secondary: Not reported	Primary: LDL-C was significantly reduced by 32.6, 31.0 and 30.3% after three, six and 12 months, respectively (P value not reported). HDL-C was significantly increased by 3.1, 5.9 and 2.6% after three, six and 12 months, respectively. In patients with baseline HDL-C <40 mg/dL, HDL-C increased by 16.2, 22.4 and 19.0% after three, six and 12 months (P values not reported). Remnant-like particle cholesterol were significantly reduced by 14.0, 20.2 and 22.8% after three, six and 12 months, respectively (P value not reported). TG was significantly reduced by 17.7 and 15.9% after three and 12 months, respectively, in patients whose baseline TG >150 mg/dL, although TG was not significantly reduced in the overall population (P value not reported). hsCRP were significantly reduced in 31 patients after 12 months (P<0.01). hsCRP was significantly reduced in patients with diabetes (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported
Motomura et al.[31] (2009) Pitavastatin 2 mg/day	MC, OL, PRO Patients >20 years of age with type 2 diabetes, LDL-C ≥120 mg/dL, TG <400 mg/dL, HbA_{1c} <9.0% and not on hypolipidemic medication for the preceding 4 weeks	N=65 6 months	Primary: Changes from baseline in lipid panel and hsCRP Secondary: Not reported	Primary: Significant reductions in TC, LDL-C and TG and significant increases in HDL-C were observed at one, three and six months after treatment with pitavastatin was initiated (P<0.05 for all). After six months, average reductions in TC, LDL-C and TG were: 27.1, 41.1 and 6.2%. Average increase in HDL-C at six months was 4.5%. Changes in hsCRP were not significant after three months of treatment (0.49 to 0.43 mg/L; P=0.057), but was significantly reduced at six months (0.49 to 0.37 mg/L; P<0.05). Secondary: Not reported
Ose et al.[32] (2010) Pitavastatin 4 mg QD	ES, OL Patients with primary hypercholesterolemia or combined dyslipidemia who had previously received pitavastatin, atorvastatin or simvastatin for 12 weeks during a DB, Phase III trial	N=1,353 52 weeks	Primary: Safety and tolerability Secondary: Proportion of patients achieving NCEP and European Atherosclerosis Society LDL-C goals (not specified), changes from baseline in lipid profiles	Primary: Overall, 54.8% of patients reported experiencing at least one treatment emergent adverse event, 12.0% of which were determined by the investigators to be related to pitavastatin. Furthermore, 4.1% (n=55) of patients discontinued due to treatment emergent adverse events and 3.6% (n=49) of patients experienced a serious treatment emergent adverse event, none of which were related to pitavastatin. Two patients died during the trial, neither of which were determined to be related to pitavastatin. The most commonly reported adverse events were increased CK levels (5.8%), nasopharyngitis (5.4%) and myalgia/myalgia intercostals (4.1%). Secondary: At the end of the original DB phases, 71.5 and 69.4% of patients had achieved the LDL-C goals. After 52 weeks, 74.0 and 73.5% of patients achieved the goals. The reductions in mean LDL-C observed at the end of the DB phases were sustained throughout the ES. HDL-C showed a gradual increase; mean HDL-C at week 52 was 57.0 mg/dL (equivalent to a mean change of 14.3% above baseline and 8.7% above end of the DB phases; P value not reported). Non-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				HDL-C was associated with a sustained decrease from baseline during the ES (38.9% at end of DB phases and 39.6% at week 52). Concentrations of TG, TC, apo AI, apo B, TC:HDL-C, non-HDL-C:HDL-C and apo B:AI were similar at the end of the ES to those observed at the end of the DB phases.
Stein et al.[33] (2007) Rosuvastatin 40 mg/day for ≤96 weeks All patients entered a 6 week dietary lead in period.	MC, OL Patients ≥18 years of age with LDL-C ≥190 to ≤260 mg/dL and TG <400 mg/dL	N=1,380 ≤96 weeks	Primary: Percentage of patients who achieved NCEP ATP III LDL-C goals (<160, <130 or <100 mg/dL) at 12 weeks Secondary: Reduction in LDL-C, HDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B	Primary: At 12 weeks, 83% of patients achieved an LDL-C goal (95% CI, 81 to 85; P value not reported). Secondary: At 48 weeks, rosuvastatin was associated with a significant reduction from baseline in LDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B (P<0.0001). At 48 weeks, rosuvastatin was associated with a significant increase from baseline in HDL-C (11%; P<0.0001). During the 96-week trial period, 13.0% of patients experienced a serious adverse event, 0.4% of these patients died and 2.0% experienced myalgia (P value not reported).
Preston et al.[34] (2007) RESPOND Amlodipine 5 or 10 mg QD plus atorvastatin 10, 20, 40 or 80 mg QD (all possible dosing combinations) vs	DB, RCT Patients 18 to 75 years of age with HTN and dyslipidemia	N=1,660 8 weeks	Primary: Mean change from baseline in SBP and LDL-C Secondary: Augmentation of BP lowering with the addition of atorvastatin and augmentation of LDL-C	Primary: Regardless of dose, combination therapy was associated with significantly greater reductions in SBP compared to atorvastatin (P<0.001 for all comparisons). Overall, combination therapy and atorvastatin achieved comparable decreases in LDL-C. Only the combination of amlodipine 5 mg plus atorvastatin 10 mg achieved significant reductions in LDL-C compared to atorvastatin 10 mg (P=0.007). Secondary: Regardless of dose, there was no difference in terms of SBP lowering between combination therapy and amlodipine (P>0.05 for all comparisons). Regardless of dose, combination therapy significantly reduced LDL-C compared to amlodipine (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
amlodipine 5 or 10 mg QD vs atorvastatin 10, 20, 40 or 80 mg QD vs placebo			lowering with the addition of amlodipine, reduction in 10 year Framingham risk scores, adverse effects	A maximal reduction in 10 year Framingham risk scores was observed with combination therapy (5/80 and 10/80 mg; P values not reported). The proportion of patients who discontinued therapy due to adverse effects was similar with all treatments (5.6 vs 5.4 vs 4.1, respectively; P value not reported).
Ballantyne et al.[35] (2003) Ezetimibe 10 mg QD and atorvastatin 10 to 80 mg QD vs ezetimibe 10 mg QD vs atorvastatin 10 to 80 mg QD vs placebo	DB, PC, RCT Men and women aged ≥18 years with primary hypercholesterolemia (LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL)	N=628 12 weeks	Primary: Percentage reduction in direct LDL-C from baseline to final assessment Secondary: Change from baseline to final assessment for calculated LDL-C, TC, TG, HDL-C, TC:HDL-C ratio, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, Lp(a), direct LDL-C:HDL-C ratio, adverse events	Primary: There was a significantly greater mean reduction of direct LDL-C from baseline to final assessment in the ezetimibe plus atorvastatin group compared to either atorvastatin alone (P<0.01) or ezetimibe alone (P<0.01). Mean changes in direct LDL-C ranged from -50 to -60% in the combination group compared to -35 to -51% in the atorvastatin alone group (P<0.01). Secondary: Calculated LDL-C was also significantly reduced more commonly in the combination group than all doses of atorvastatin monotherapy (P<0.01). Greater reductions in LDL-C, TC, and TG were observed with increasing doses of atorvastatin monotherapy. However, there was not a favorable dose response with HDL-C. There were similar reductions in LDL-C (50 vs 51%), TC:HDL-C ratio (43 vs 41%), and TG (both 31%) with coadministration of ezetimibe plus atorvastatin 10 mg and the maximal dose of atorvastatin monotherapy, respectively. However, there was a significantly greater increase in HDL-C (9 vs 3%) with the combination group. Reductions in apo B, non–HDL-C, and direct LDL-C:HDL-C ratio from baseline were significantly greater in the combination group compared to both atorvastatin monotherapy (P<0.01 for all) and ezetimibe monotherapy (P<0.01 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				However, increases in HDL_2-C (P=0.53), HDL_3-C (P=0.06), apo AI (P=0.31), and Lp(a) (P=0.50) did not significantly differ between the combination therapy and atorvastatin monotherapy groups. There also was no significant difference between the combination therapy and ezetimibe monotherapy groups for increases in these same parameters: HDL_2-C (P=0.08), HDL_3-C (P=0.67), apo AI (P=0.80), and Lp(a) (P=0.92). The combination of ezetimibe plus atorvastatin was well-tolerated. Treatment-emergent adverse events were reported in 17% of patients receiving atorvastatin monotherapy and 23% of patients receiving combination therapy. The majority of adverse events were mild to moderate in severity.
Stein et al.[36] (2004) Ezetimibe 10 mg QD and atorvastatin 10 mg QD (titrated up to 40 mg/day) vs atorvastatin 20 mg QD (titrated up to 80 mg/day)	DB, DD, MC Patients ≥18 years of age with primary hypercholesterolemia and documented CHD, ≥2 cardiovascular risk factors, or heFH with an LDL-C level ≥130 mg/dL despite treatment with atorvastatin 10 mg	N=621 14 weeks	Primary: Percentage of patients achieving an LDL-C level ≤100 mg/dL after 14 weeks randomization Secondary: Effects on other lipid parameters four weeks after randomization	Primary: When compared to atorvastatin monotherapy, a significantly higher percentage of patients in the ezetimibe and atorvastatin reached an LDL-C level ≤100 mg/dL after 14 weeks randomization, respectively (7 vs 22%; P<0.01). Secondary: When compared to atorvastatin monotherapy, significant reductions in LDL-C, TC and TG levels were observed in patients in the ezetimibe and atorvastatin (P<0.01). Respectively, percent changes between combination vs atorvastatin monotherapy were -22.8 vs -8.6% (mean change) in LDL-C levels, -17.3 vs -6.1% in TC levels (mean change), and -9.3 vs -3.9% (median change) in TG levels (P<0.01 for all). Nonsignificant changes were observed in HDL-C levels.
Conard et al.[37] (2008) Ezetimibe 10 mg QD and atorvastatin 20 mg QD vs	DB, MC, PG, RCT Patients 18 to 79 years of age at moderately high risk for CHD who were receiving atorvastatin 20	N=196 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <100 mg/dL,	Primary: Treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-31 vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe plus atorvastatin achieved the NCEP ATP III LDL-C goal <100 mg/dL compared to atorvastatin 40 mg (84 vs 49%, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 40 mg QD	mg QD with LDL-C levels of 100 mg/dL to 160 mg/dL and TG ≤350 mg/dL		percent change TG, TC, HDL-C, non-HDL-C, apo AI, apo B, TC: HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C, hsCRP	Treatment with ezetimibe plus atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C than treatment with atorvastatin 40 mg (P<0.001). There was no significant difference in HDL-C, TG, apo AI, and hsCRP among the treatment groups.
Leiter et al.[38] (2008) Ezetimibe 10 mg QD and atorvastatin 40 mg QD vs atorvastatin 80 mg QD	DB, MC, PG, RCT Patients 18 to 79 years of age at high risk for CHD (CHD or those with a CHD risk equivalent medical condition) who were receiving atorvastatin 40 mg QD with LDL-C levels of 70 mg/dL to 160 mg/dL and TG ≤350 mg/dL	N=579 6 weeks	Primary: Percent change in LDL-C Secondary: Percentage of patients achieving LDL-C <70 mg/dL, percent change TG, TC, HDL-C, non-HDL-C, apo AI, apo B, TC: HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C, hsCRP	Primary: Treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to doubling the dose of atorvastatin (-27 vs -11%, respectively; P<0.001). Secondary: Significantly more patients treated with ezetimibe plus atorvastatin achieved the NCEP ATP III LDL-C goal <70 mg/dL compared to atorvastatin 80 mg (74 vs 32%, respectively; P<0.001). Treatment with ezetimibe plus atorvastatin led to greater improvements in non-HDL-C, TC, apo B, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C compared to atorvastatin 80 mg (P<0.001). There was no significant difference in HDL-C, TG, apo AI, and hsCRP among the treatment groups.
Zieve et al.[39] (2010) ZETELD Ezetimibe 10 mg QD for 12 weeks and atorvastatin 10 mg QD for 6	DB, MC, PG, RCT Patients ≥65 years of age at high risk for CHD with or without atherosclerotic	N=1,053 12 weeks	Primary: Percent change in LDL-C after six weeks Secondary: Percentage of patients	Primary: After six weeks of therapy, treatment with ezetimibe plus atorvastatin led to a significantly greater reduction in LDL-C compared to atorvastatin monotherapy (-29 vs -15%; P<0.001). Secondary: The percentage of patients achieving LDL-C <70 mg/dL and LDL-C <100 mg/dL (without AVD) or <70 mg/dL (with AVD) was significantly greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
weeks, followed by atorvastatin 20 mg QD for 6 weeks vs atorvastatin 20 mg QD for 6 weeks, followed by atorvastatin 40 mg for 6 weeks	vascular disease who had not reached a LDL-C <70 mg/dL or <100 mg/dL, respectively, after receiving atorvastatin 10 mg/day		achieving LDL-C <70 mg/dL and <100 mg/dL for high-risk patients without AVD and <70 mg/dL for high-risk patients with AVD, HDL-C, non-HDL-C, TG, TG, apo B, apo AI, TC:HDL-C, apo B:apo AI, LDL-C:HDL-C, non-HDL-C:HDL-C	with ezetimibe plus atorvastatin compared to atorvastatin monotherapy at week six and week 12 (P<0.001). After six weeks of therapy, treatment with ezetimibe plus atorvastatin led to significantly greater changes in HDL-C (+3 vs +1%; P=0.02), TC (-16 vs -8%; P<0.001), non-HDL-C (-24 vs -11%; P<0.001), TG (-13 vs -6%; P<0.001), apo B (-17 vs -8%; P<0.001), TC:HDL-C (-17 vs -8%; P<0.001), LDL-C:HDL-C (-27 vs -13%; P<0.001), apo B:apo AI (-15 vs -5%; P<0.001), and non- HDL-C:HDL-C (-24 vs -11%; P<0.001). At week 12, significantly greater changes in favor of ezetimibe plus atorvastatin occurred in HDL-C, TC, non-HDL-C, apo B, apo AI, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C. There was no significant difference among the treatment groups in apo AI at week six, high-sensitivity C-reactive protein at weeks six and 12, and TG at week 12.
Piorkowski et al.[40] (2007) Atorvastatin 40 mg QD vs atorvastatin 10 mg QD and ezetimibe 10 mg QD	RCT Patients 18 to 80 years of age with clinically stable angiographically documented CHD and LDL-C >2.5 mmol/L despite ongoing atorvastatin 10 to 20 mg/day, receiving aspirin and clopidogrel	N=56 4 weeks	Primary: Change in liver transaminases, CK, HDL-C, LDL-C, and TG from baseline, percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L) Secondary: Not reported	Primary: There were no statistically significant differences from baseline in liver transaminases, CK, or HDL-C in either group. Both groups exhibited a statistically significant reduction in LDL-C from baseline (P<0.005). There was no statistically significant difference between the two groups in degree of LDL-C reduction from baseline. Both the atorvastatin 40 mg and the combination therapy groups exhibited a statistically significant reduction in TG level from baseline (P<0.005 and P<0.05, respectively). There was no statistically significant difference between the two groups in the percentage of patients achieving the NCEP ATP III LDL-C goal (≤2.5 mmol/L). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Not reported
Goldberg et al.[41] (2006) VYTAL Atorvastatin 10, 20, or 40 mg/day vs simvastatin 20 or 40 mg/day and ezetimibe 10 mg/day daily	DB, MC, PG, RCT Adult patients with type 2 diabetes between 18 and 80 years of age with HbA_{1c} ≤8.5%, LDL-C >100 mg/dL and a TG level <400 mg/dL	N=1,229 6 weeks	Primary: Percent reduction in LDL-C level at week six Secondary: Proportion of patients who achieved the NCEP ATP III LDL-C goal (<70 mg/dL), proportion of patients who achieved LDL-C level of <100 mg/dL, percent change from baseline in HDL-C, non-HDL-C, TC, TG, and CRP	Primary: Patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week six of the study compared to patients receiving atorvastatin 10 or 20 mg (53.6, 38.3, and 44.6%, respectively; P<0.001). Patients randomized to simvastatin 40 mg plus ezetimibe 10 mg combination therapy experienced a greater reduction in LDL-C from baseline at week six of the study compared to patients receiving atorvastatin 40 mg (57.6 and 50.9%, respectively; P<0.001). Secondary: A greater proportion of patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination therapy achieved LDL-C <70 mg/dL compared to patients receiving atorvastatin 10 or 20 mg (59.7, 21.5, and 35%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 40 mg plus ezetimibe 10 mg therapy achieved LDL-C <70 mg/dL compared to patients receiving atorvastatin 40 mg (74.4 and 55.2%, respectively; P<0.001). A greater proportion of patients randomized to simvastatin 20 mg plus ezetimibe 10 mg therapy achieved LDL-C <100 mg/dL compared to patients receiving atorvastatin 10 or 20 mg (90.3, 70, and 82.1%, respectively; P=0.007). A greater proportion of patients randomized to simvastatin 40 mg plus ezetimibe 10 mg therapy achieved LDL-C <100 mg/dL compared to patients receiving atorvastatin 40 mg (93.4 and 88.8%, respectively; P=0.07). Patients randomized to simvastatin plus ezetimibe combination therapy, at all doses, experienced a significant increase in HDL-C level (P≤0.001), a greater reduction in TC, and non-HDL-C (P<0.001) compared to patients receiving atorvastatin, at all doses. Patients randomized to simvastatin 20 mg plus ezetimibe 10 mg combination

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				therapy experienced a significant reduction in CRP and TG level compared to patients receiving atorvastatin (P=0.02). Side effects were similar in the simvastatin plus ezetimibe and atorvastatin groups (19.85 vs 22.7%).
Winkler et al.[42] (2007) Fluvastatin 20 mg, 40 mg, and 80 mg (pooled group) vs placebo	MA (30 trials) DB, PC, RCTs assessing ≥6 weeks of fluvastatin therapy in dyslipidemic patients with and without metabolic syndrome	N=7,043 ≥6 weeks	Primary: Major adverse cardiovascular events defined as cardiovascular disease-related death, nonfatal MI, and cardiac re-vascularization, LDL-C, HDL-C, TC, TG, non-HDL-C, apo B Secondary: Not reported	Primary: Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of any major adverse cardiovascular events compared to placebo (16 vs 22%; HR, 0.728; 95% CI, 0.6 to 0.9; P=0.001). The difference in the incidence of major adverse cardiovascular events between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.083). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death compared to placebo (3 vs 4.9%; HR, 0.62; 95% CI, 0.4 to 0.95; P=0.03). The difference in the incidence of cardiovascular death between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.478). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular intervention compared to placebo (12 vs 16%; HR, 0.75; 95% CI, 0.59 to 0.93; P=0.011). The difference in the incidence of cardiovascular intervention between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.125). Among patients with metabolic syndrome, pooled fluvastatin was associated with a statistically significant reduction in the risk of a cardiovascular death or nonfatal MI compared to placebo (6.6 vs 9.9%; HR, 0.65; 95% CI, 0.48 to 0.87; P=0.005). The difference in the incidence of cardiovascular death or nonfatal MI between fluvastatin- and placebo-treated patients without metabolic syndrome was not statistically significant (P=0.288). There was no statistically significant difference in the incidence of nonfatal MI, all-cause mortality, or non-cardiovascular-related death between pooled fluvastatin- and placebo-treated patients whether or not they had the metabolic

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				syndrome (P>0.05). In all patients, pooled fluvastatin was associated with a significant reduction from baseline in LDL-C, TC, TG, non-HDL-C, and apo B compared to placebo (P<0.001). Patients with and without the metabolic syndrome taking fluvastatin experienced similar benefits in terms of LDL-C, TC, non-HDL-C, and apo B reduction from baseline. Patients with the metabolic syndrome experienced a greater increase in HDL-C and a greater reduction in TG from baseline compared to patients without the metabolic syndrome (P<0.01). Secondary: Not reported
Stein et al.[43] (2008) Fluvastatin XL 80 mg QD vs ezetimibe 10 mg QD vs fluvastatin XL 80 mg QD and ezetimibe 10 mg QD	DB, MC, PG, RCT Patients ≥18 years of age with dyslipidemia who had previously documented muscle related side effects that had led to cessation of statin treatment or patients currently receiving statin treatment whose quality of life was affected by muscle related side effects and	N=218 12 weeks	Primary: Percent decrease in LDL-C Secondary: LDL:HDL-C, TC, TG, apo B, proportion of patients achieving LDL-C goal	Primary: LDL-C was reduced by 15.6, 32.8, and 46.1% with ezetimibe monotherapy, fluvastatin XL monotherapy, and fluvastatin XL plus ezetimibe combination therapy, respectively (fluvastatin XL vs ezetimibe: -17.1%; P<0.0001; fluvastatin XL plus ezetimibe vs ezetimibe: -30.4%; P<0.0001). Secondary: Treatment with fluvastatin XL monotherapy and fluvastatin XL plus ezetimibe combination therapy led to a greater reduction in LDL:HDL-C, TC, TG, and apo B levels compared to ezetimibe monotherapy (all, P<0.0001). More patients achieved their target LDL-C goal with fluvastatin XL monotherapy and fluvastatin XL plus ezetimibe combination therapy compared to ezetimibe monotherapy (P<0.001 for fluvastatin XL monotherapy or combination therapy vs ezetimibe monotherapy). There were no serious adverse events, rhabdomyolysis, or creatine kinase increases ≥10 times upper limit of normal. Muscle related side effects were reported in 24% of patients receiving ezetimibe monotherapy compared to 17% of patients in the fluvastatin XL group and 14% of patients in the fluvastatin XL plus ezetimibe combination group. Differences in recurrence of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	required switching to an alternative treatment			muscle related side effects were not statistically different between treatment groups.
Alvarez-Sala et al.[44] (2008) Fluvastatin XL 80 mg QD (nighttime) and ezetimibe 10 mg QD vs fluvastatin XL 80 mg QD (nighttime)	MC, OL, PG, RCT Patients 18 to 75 years of age with primary hypercholesterolemia (LDL-C ≥130 mg/dL and TG ≤400 mg/dL)	N=89 12 weeks	Primary: Percentage change in LDL-C Secondary: Percentage change in HDL-C and TG, proportions of patients achieving NCEP ATP III LDL-C goals, change in hsCRP and other markers of inflammation, and safety	Primary: Fluvastatin XL plus ezetimibe lowered mean LDL-C from 197 mg/dL to 97 mg/dL (-49.9%) and fluvastatin XL alone lowered mean LDL-C from 216 to 135 mg/dL (-35.2%) after 12 weeks of therapy (P<0.001). Secondary: Fluvastatin XL plus ezetimibe combination was associated with a significantly greater reduction from baseline in TC, TG, and apo B than fluvastatin XL alone (P<0.05 for all). There was no significant change in HDL-C level with either treatment regimen. A greater proportion of patients receiving the fluvastatin XL plus ezetimibe achieved NCEP ATP III LDL-C goals at week 12 compared to those receiving fluvastatin XL alone (86.5 vs 66.7%; P=0.042). There were no significant changes in levels of hsCRP with either treatment regimen. In patients with higher baseline hsCRP levels, the coadministration of fluvastatin XL with ezetimibe was associated with a reduced level of this inflammatory marker. Treatment with fluvastatin XL plus ezetimibe or fluvastatin XL alone was associated with significant reductions in IL-1β (21%; P<0.001 and 13%; P<0.002, respectively). No significant changes were seen in levels of interleukin-6, tumor necrosis factor-α, soluble P-selectin, or soluble vascular cell adhesion molecule-1. There was no significant difference in the incidence of adverse events between the treatment groups. Most adverse events were mild or moderate in intensity, with headache being the most common (8.5%).
Messerli et al.[45] (2006) AVALON	DD, MC, OL, RCT Patients with	N=847 28 weeks	Primary: Proportion of patients who reached the	Primary: A significantly greater proportion of patients receiving combination therapy achieved JNC 7 and NCEP ATP goals at eight weeks compared to patients receiving amlodipine or patients receiving atorvastatin monotherapy (45.0 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Amlodipine 5 mg/day for 8 weeks, followed by the addition of atorvastatin 10 mg/day for another 8 weeks vs atorvastatin 10 mg/day for 8 weeks, followed by the addition of amlodipine 5 mg/day for an additional 8 weeks vs amlodipine-atorvastatin 5-10 mg/day for 16 weeks vs placebo for 16 weeks All patients received an additional 12 weeks of OL treatment following the first	HTN and dyslipidemia		JNC 7 and NCEP ATP III goals, side effects Secondary: Not reported	8.3 and 28.6%, respectively; P<0.001). The incidence of side effects was similar across all treatments (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
16 weeks of therapy.				
Hunninghake et al.[46] (2001) Colesevelam 3.8 g/day vs atorvastatin 10 mg/day vs colesevelam 3.8 g/day plus atorvastatin 10 mg/day vs atorvastatin 80 mg/day vs placebo	DB, MC, PC, RCT Patients with LDL-C ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in TC, HDL-C, TG, apo B, apo AI and Lp(a)	Primary: All treatments resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions from baseline were -12% with colesevelam (P<0.05), -38% with atorvastatin 10 mg (P<0.0001), -48% with colesevelam plus atorvastatin (P<0.0001) and -53% with atorvastatin 80 mg (P<0.0001), respectively. Secondary: Colesevelam reduced TC by six percent (P<0.05), increased HDL-C by three percent (P<0.05) and increased TG by 10% (P value not reported). Atorvastatin 10 mg reduced TC by 27% (P<0.0001), increased HDL-C by eight percent (P<0.05) and reduced TG by 24% (P<0.05). Colesevelam plus atorvastatin reduced TC by 31% (P<0.0001), increased HDL-C by 11% (P<0.05) and reduced TG by one percent (P value not reported). Atorvastatin 80 mg reduced TC by 39% (P<0.0001), increased HDL-C by five percent (P<0.05) and reduced TG by 33% (P<0.0001). Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam plus atorvastatin. No significant differences in HDL-C were found between the treatment groups (P values not reported). Apo B levels decreased significantly for with all treatments relative to baseline (P<0.01). No significant changes in apo AI and Lp(a) were reported (P values not reported).
Brown et al.[47] (1990) Colestipol 5 to 10 g TID plus niacin 125 mg BID titrated to 1 to 1.5 g TID	DB, RCT Men ≤62 years of age with elevated apo B and a family history of CAD	N=120 32 months	Primary: Average change in the percent stenosis for the worst lesion in each of the nine proximal segments	Primary: On average, placebo (conventional therapy) increased the index of stenosis by 2.1 percentage points a baseline of 34%. By contrast, it decreased by 0.7 percentage points with colestipol plus lovastatin and by 0.9 percentage points with colestipol and niacin (P<0.003 for trend). At trial end, on average, these nine lesions were almost 3 percentage points less severe among patients treated intensively compared to conventionally. This difference represents almost 1/10 of the amount of disease present at baseline (34% stenosis).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs Colestipol 5 to 10 g TID plus lovastatin 20 mg BID titrated to 40 mg BID vs placebo (or colestipol if LDL-C was elevated)			Secondary: Average changes in all lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease when looking at the effect of treatment on certain subsets of lesions (all lesions measured in each patient, lesions causing severe or mild stenosis and those that did not cause total occlusion at baseline). The results with both treatment groups were significantly difference from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.
Kerzner et al.[48] (2003) Ezetimibe 10 mg/day vs lovastatin 10, 20 or 40 mg/day vs ezetimibe 10 mg/day plus lovastatin 10, 20 or 40 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with mean plasma LDL-C 145 to 250 mg/dL as calculated by Friedewald equation and mean TG ≤350 mg/dL	N=548 12 weeks	Primary: Percentage decrease from baseline in LDL-C Secondary: Changes from baseline in calculated LDL-C, TC, TG, HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, apo AI and LDL-C:HDL-C; adverse events	Primary: The reduction in LDL-C was significantly greater with combination therapy compared to either lovastatin or ezetimibe (P<0.01 for both). The mean percentage decrease in LDL-C with combination therapy was significantly greater than the decrease obtained from the corresponding lovastatin dose or next higher dose of lovastatin (P<0.01). The mean percentage change in LDL-C achieved with combination therapy (lovastatin 10 mg) was similar to lovastatin 40 mg (P=0.10). Secondary: In comparison to lovastatin, combination therapy significantly improved calculated LDL-C, TC, TG, HDL-C, apo B, non-HDL-C, HDL_2-C, HDL_3-C, LDL-C:HDL-C (P<0.01 for all) and apo AI (P=0.04). Combination therapy significantly increased HDL-C with lovastatin doses of 20 and 40 mg compared to the same lovastatin dose administered as monotherapy (P<0.01 and P<0.02, respectively), and significantly decreased TG levels (P<0.01 for both). Treatment-related adverse events were reported by 16% of patients receiving lovastatin and 17% of patients receiving combination therapy. The safety profile for combination therapy was similar to that for lovastatin and placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				(P values not reported).
Lewis et al.[49] (2007) Pravastatin 80 mg QD vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with hypercholesterolemia, LDL-C ≥100 and TG <400 mg/dL, with ≥6 month history of compensated liver disease	N=326 36 weeks	Primary: Percent change from baseline at week 12 in LDL-C, TC and TG; ALT event rate (ALT at least two times the upper limit of normal for those with normal ALT at baseline or a doubling of the baseline ALT for those with elevated ALT at baseline) Secondary: Not reported	Primary: Pravastatin was associated with a significant reduction in LDL-C, TC and TG at week 12 compared to placebo (P<0.0001). There was no significant difference between the two treatments in the ALT event rate at any time during the trial (P>0.05). By week 36, 7.5 and 12.5% of patients receiving pravastatin and placebo had at least one ALT event (P=0.1379). Secondary: Not reported
Melani et al.[50] (2003) Ezetimibe 10 mg/day vs pravastatin 10, 20 or 40 mg/day vs ezetimibe 10 mg/day plus	DB, MC, PC, RCT Patients 20 to 86 years of age with primary hypercholesterolemia (LDL-C 3.8 to 6.5 mmol/L as calculated by the Friedewald equation and TG ≤4.0 mmol/L)	N=538 12 weeks	Primary: Percent change from baseline LDL-C Secondary: Mean and percent changes from baseline in calculated LDL-C, TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C,	Primary: A mean percent change of -38 and -24% in LDL-C with combination therapy and pravastatin were observed (P<0.01). Combination therapy achieved a mean percentage change in LDL-C ranging from -34 to -41% compared to -20 to -29% with pravastatin (all doses). When combination therapy was compared to its corresponding pravastatin dose, the incremental mean percentage reductions in LDL-C were significant in favor of combination therapy (P≤0.01). In addition, combination therapy (pravastatin 10 mg) produced a larger mean percentage reduction in LDL-C compared to pravastatin 40 mg (P≤0.05). Secondary: In comparison to pravastatin, combination therapy improved calculated LDL-C, TG, TC, apo B, non-HDL-C, LDL-C:HDL-C and TC:HDL-C (P<0.01 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
pravastatin 10, 20 or 40 mg/day vs placebo			apo AI, apo B, HDL_2-C, HDL_3-C and Lp(a)	all). Both direct and calculated LDL-C levels at all pravastatin doses were significantly reduced with combination therapy (P<0.01). TG was also significantly reduced with combination therapy (pravastatin 10 and 20 mg) compared to pravastatin (P<0.05). Although combination therapy (pravastatin 10 and 40 mg) produced greater increases in HDL-C, it was not significant (P values not reported). The differences in change in HDL_2-C, HDL_3-C, apo AI and Lp(a) between combination therapy and pravastatin were not significant (P values not significant). Combination therapy was well tolerated and the overall safety profile was similar to pravastatin and placebo. There was no evidence to suggest that combination therapy would increase the risk of developing any nonlaboratory adverse event (P value not reported).
Coll et al.[51] (2006) Ezetimibe 10 mg/day vs fluvastatin XR 80 mg/day	RCT Patients ≥18 years of age with HIV receiving stable HAART for ≥6 months and fasting LDL-C ≥3.30 mmol/L	N=20 6 weeks	Primary: LDL-C, TC, endothelial function Secondary: Not reported	Primary: Ezetimibe produced a 20% (P=0.002) LDL-C reduction and a 10% TC reduction (P=0.003). Fluvastatin XR produced a 24% (P=0.02) LDL-C reduction and a 17% TC reduction (P=0.06). There were no significant differences in lipid lowering ability between the two treatments (P values not reported). Ezetimibe did not produce significant changes in endothelial function, while fluvastatin XR produced an increase in the rate of endothelial function by 11% (P=0.5). Secondary: Not reported
Illingworth et al.[52] (1994) Lovastatin 10 to 80 mg/day vs	MC, OL, RCT Patients 21 to 75 years of age with primary hypercholesterolemia and either an LDL-C >160	N=136 26 weeks	Primary: Change from baseline in lipid parameters Secondary: Safety	Primary: Lovastatin reduced TC, LDL-C and apo B significantly more than niacin (P<0.01 for all). At weeks 10, 18 and 26, LDL-C was reduced by 26, 28 and 32% with lovastatin compared to five, 16 and 21% with niacin, respectively. The target treatment goal of LDL-C <130 mg/day for patients with CHD or less than two risk factors was achieved in 14, 19 and 35% of patients receiving lovastatin compared to zero, 18 and 26% of patients receiving placebo at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
niacin IR 0.25 mg to 1.5 g TID	mg/dL and CHD or ≥2 CHD risk factors without CHD or LDL-C >190 mg/dL without CHD or ≥2 risk factors after rigorous diet			weeks 10, 18 and 26, respectively (P values not significant). For the majority of those patients with CHD or two or more risk factors in whom the LDL-C goal was <110 mg/dL, neither drug was effective in achieving this goal. In these patients only 13 and 11% achieved this goal at week 26, respectively (P value not reported). Niacin was more effective in decreasing TG at week 26 (P<0.01 vs lovastatin). Both treatments were effective in reducing VLDL-C, with no significant difference observed between the two treatments (P value not reported). Niacin produced reductions in Lp(a) of 14, 30 and 35% at weeks 10, 18 and 26, whereas lovastatin had no effect (P<0.05 or P<0.01 between drugs at each time point). Niacin was significantly more effective at increasing HDL-C and apo AI (P<0.01 vs lovastatin), except for the change in apo A1 at week 10 (P value not reported). Niacin increased HDL-C by 20, 29 and 33% and apo AI by 11, 19 and 22% at weeks 10, 18 and 26. Lovastatin resulted in a modest increase in HDL-C and apo AI of 7 and 6%, respectively, at week 26. Secondary: Four deaths occurred in the trial, one with niacin and three with lovastatin. All were related to atherosclerosis, and none were deemed to be drug-related. Five and nine patients receiving lovastatin and niacin discontinued treatment because of adverse experiences (excluding deaths). For those who discontinued treatment, the reason was considered drug-related in four and eight patients receiving lovastatin and niacin (P value not significant). The major reasons for discontinuation of niacin were cutaneous complaints, including flushing, pruritis and rash. One patient discontinued lovastatin because of myalgias. Overall, patient tolerance to the treatments was better with lovastatin. Adverse events (in decreasing frequency) that occurred more frequently with niacin include flushing, paresthesia, pruritis, dry skin, nausea/vomiting, asthenia and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				diarrhea.
Eriksson et al.[53] (1998) Cholestyramine 16 g/day vs cholestyramine 8 g/day plus pravastatin 20 mg/day vs pravastatin 20 or 40 mg/day	MC, RCT Patients 30 to 65 years of age	N=2,036 12 months	Primary: Percent change from baseline in LDL-C Secondary: Compliance	Primary: Percent changes in LDL-C from baseline to endpoint with cholestyramine, cholestyramine plus pravastatin, pravastatin 20 mg and pravastatin 40 mg were -26 (95% CI, -23 to -29), -36 (95% CI, -33 to -39), -27 (95% CI, -25 to -29) and -32% (95% CI, -30 to -34). Secondary: Compliance rates with cholestyramine, cholestyramine plus pravastatin, pravastatin 20 mg and pravastatin 40 mg were 44, 53, 76 and 78% (P values not reported). Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common with cholestyramine and cholestyramine plus pravastatin.
Hing Ling et al.[54] (2012) Atorvastatin 40 mg/day vs ezetimibe 10 mg/day plus simvastatin 40 mg/day All patients received atorvastatin 20 mg/day for six weeks at baseline.	AC, DB, MC, RCT Patients 18 to 79 years of age at high risk for CHD with primary hypercholesterolemia, LDL >100 mg/dL and <160 mg/dL, triglycerides <350 mg/dL, liver function tests within normal limits without active liver disease	N=250 6 weeks	Primary: Change from baseline in LDL-C, Secondary: TC, HDL, CRP, Apo AI, Apo B, TG, non-HDL, LDL-C/HDL ratio, TC/HDL ratio, non-HDL/HDL ratio, Apo AI/Apo B ratio	Primary: After six weeks, treatment with ezetimibe/simvastatin resulted in significantly greater reductions from baseline in LDL-C levels compared to treatment with atorvastatin 40 mg (-26.8 vs -11.8%; P<0.001). Secondary: Treatment with ezetimibe/simvastatin resulted in significantly greater reductions in TC (P<0.001), non-HDL-C (P<0.001), Apo B (P=0.002), Apo AI (P<0.001), and all lipid ratios (P<0.001 for all). There were no significant differences between treatments with regard to the change from baseline in TG (P=0.593), HDL-C (P=0.211), or CRP (P=0.785).
Pearson et al.[55]	MA (1 AC, DB; 3	N=4,373	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2007) Atorvastatin 10, 20, 40 or 80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs placebo	PRO) Patients with primary hypercholesterolemia	 12 weeks	Change from baseline in LDL-C level and hsCRP, proportion of patients reaching LDL-C target (<100 or <70 mg/dL) Secondary: Not reported	Across all doses, combination therapy was associated with significant reductions in LDL-C compared to simvastatin (52.5 vs 38.0%; P<0.001) and atorvastatin (53.4 vs 45.3%; P<0.001). Across all doses, combination therapy was associated with significant reductions in hsCRP compared to simvastatin (31.0 vs 14.3%; P<0.001). No significant difference was observed between combination therapy and atorvastatin (25.1 vs 24.8%; P value not reported). The reduction in hsCRP was not significantly different between simvastatin 10 mg and placebo (P>0.10). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL compared to simvastatin (78.9 vs 43.1%; P<0.001) and atorvastatin (79.8 vs 61.9%; P<0.001). Similar results were observed with an LDL-C goal <70 mg/dL (37.0 vs 5.7%; P<0.001 and 36.2 vs 16.8%; P<0.001). Secondary: Not reported
Winkler et al.[56] (2009) Fluvastatin 80 mg/day plus fenofibrate 200 mg/day vs	MC, OL, RCT, XO Patients 18 to 75 years of age with metabolic syndrome, low HDL-C, waist circumference	N=75 6 weeks	Primary: Changes from baseline in lipids, lipoproteins and apolipoproteins; LDL subfractions	Primary: Reductions in TC, LDL-C and apo B were greater with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate, but differences only reached significance in patients without small, dense LDL (P=0.043, P=0.006 and P=0.20). Reductions in TG were only significant with fluvastatin plus fenofibrate compared to ezetimibe plus simvastatin in patients with small, dense LDL (P=0.029). Increases in HDL-C and apo AI were only significant with ezetimibe plus simvastatin compared to fluvastatin plus fenofibrate in patients without small, dense LDL (P=0.020 and P=0.015). In patients with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
ezetimibe 10 mg/day plus simvastatin 20 mg/day	≥94 (men) or ≥80 cm (females) plus 1 of the following: TG ≥150 mg/dL, BP (≥85/≥130 mm Hg), fasting glucose ≥100 mg/dL or prevalent type 2 diabetes		Secondary: Not reported	small, dense LDL, apo AII was markedly increased by fluvastatin plus fenofibrate, whereas ezetimibe plus simvastatin had no or little effect. Although only significant in small, dense LDL patients, apo CIII was more effectively reduce by fluvastatin plus fenofibrate, while the reduction of apo CII was more pronounced with ezetimibe plus simvastatin in all patients. Secondary: Not reported
Becker et al.[57] (2008) Simvastatin 40 mg/day plus traditional counseling vs alternative treatment (therapeutic lifestyle changes and ingestion of red yeast rice and fish oil supplements)	RCT Patients 18 to 80 years of age with hypercholesterolemia who met NCEP ATP III criteria for primary prevention using statin therapy	N=74 3 months	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in HDL-C and TG, weight loss	Primary: There was a significant reduction in LDL-C with both simvastatin (39.6±20.0%) and alternative treatment (42.4±15.0%) (P<0.001), with no significant difference noted between the two treatments (P value not reported). Secondary: Alternative treatment was associated with a significant reduction in TG compared to simvastatin (29 vs 9%; 95% CI, 61.0 to 11.7; P=0.003). No differences between the two treatments were noted in improvements with HDL-C (P=0.21). Alternative treatment was associated with a significant reduction in weight loss compared to simvastatin (5.5 vs 0.4%; 95% CI, 5.5 to 3.4; P<0.001).
Meredith et al.[58] (2007) Simvastatin 20 mg QD vs	DB, PG, RCT Patients who had undergone elective coronary angiography, had stable CAD and hsCRP >3 mg/L	N=107 16 weeks	Primary: Change from baseline in hsCRP Secondary: Change from baseline in	Primary: There was no difference between simvastatin 20 and 80 mg in terms of change from baseline in hsCRP (P=0.82). Secondary: Simvastatin, regardless of dose, was more effective than placebo in baseline reductions of LDL-C (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 80 mg QD vs placebo			LDL-C, TC and TG	Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in hsCRP (P=0.007). Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in TC (P<0.001). Simvastatin, regardless of dose, was more effective than placebo in baseline reductions in TG (P=0.01).
Knapp et al.[59] (2001) Colesevelam 3.8 g/day vs simvastatin 10 mg/day vs colesevelam 3.8 g/day plus simvastatin 10 mg/day vs colesevelam 2.3 g/day vs simvastatin 20 mg/day vs	DB, MC, PC, RCT Patients ≥18 years of age with LDL-C ≥160 mg/dL and TG ≤300 mg/dL who are not taking cholesterol lowering medication	N=258 6 weeks	Primary: Change from baseline in LDL-C Secondary: Percent change in LDL-C; mean and percent change from baseline in TC, HDL-C, TG, apo B and apo AI	Primary: LDL-C changes from baseline were -7 mg/dL with placebo (P<0.05), -31 mg/dL with colesevelam 3.8 g (P<0.0001), -48 mg/dL with simvastatin 10 mg (P<0.0001), -80 mg/dL with colesevelam 3.8 g plus simvastatin 10 mg (P<0.0001), -17 mg/dL with colesevelam 2.3 g (P<0.0001), -61 mg/dL with simvastatin 20 mg (P<0.0001) and -80 mg/dL with colesevelam 2.3 g plus simvastatin 20 mg (P<0.0001), respectively. Secondary: LDL-C percent changes from baseline were -4% with placebo (P<0.05), -16% with colesevelam 3.8 g (P<0.0001), -26% with simvastatin 10 mg (P<0.0001), -42% with colesevelam 3.8 g plus simvastatin 10 mg (P<0.0001), -8% with colesevelam 2.3 g (P<0.0001), -34% with simvastatin 20 mg (P<0.0001) and -42% with colesevelam 2.3 g plus simvastatin 20 mg (P<0.0001), respectively. Significant changes from baseline were observed for all treatments in mean and percent change in TC (P<0.0001 for all, except colesevelam 2.3 g; P<0.05). Significant changes from baseline were observed for mean and percent change in HDL-C with simvastatin 10 mg (P<0.05), colesevelam 3.8 g plus simvastatin 10 mg (P<0.0001), colesevelam 2.3 g (P<0.05), simvastatin 20 mg (P<0.05) and colesevelam 2.3 g plus simvastatin 20 mg (P<0.05). Significant changes from baseline were observed for mean and percent change in TG with colesevelam 3.8 g (P<0.05), simvastatin 10 mg (P<0.05), simvastatin 20 mg (P<0.05) and colesevelam 2.3 g plus simvastatin 20 mg (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
colesevelam 2.3 g/day plus simvastatin 20 mg/day vs placebo				Significant reductions from baseline for apo B were observed with all treatments. Reductions were significant (P<0.05) compared to placebo for all treatments except colesevelam 2.3 g (P value not reported). Significant increases in apo AI were achieved with all treatments except simvastatin 10 mg (P<0.05).
Chenot et al.[60] (2007) Simvastatin 40 mg/day vs simvastatin 40 mg/day plus ezetimibe 10 mg/day vs no lipid lowering therapy	RCT Patients admitted for an acute MI (with or without ST-segment elevation) to the coronary unit, with pain that started within 24 hours of admission	N=60 7 days	Primary: Change from baseline to days two, four and seven in LDL-C; proportion of patients achieving an LDL-C <70 mg/dL Secondary: Not reported	Primary: Combination therapy produced a significant LDL-C reduction from baseline on days two, four and seven (27, 41 and 51%, respectively; P<0.001). Simvastatin produced a significant LDL-C reduction from baseline on days two, four and seven (15, 27 and 25%, respectively; P<0.001). There was no significant reduction in LDL-C with no lipid lowering therapy (P≥0.09). Combination therapy achieved significant LDL-C reductions compared to simvastatin at days four (P=0.03) and seven (P=0.002). A greater proportion of patients receiving combination therapy achieved an LDL-C <70 mg/dL, compared to those receiving simvastatin at days four (45 vs 5%) and seven (55 vs 10%, respectively) (P values not reported). Secondary: Not reported
Davidson et al.[61] (2002) Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day	DB, MC, RCT Patients >18 years of age with primary hypercholesterolemia	N=668 20 week	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent change	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (49.9 vs 36.1%; P<0.001). Similar results were observed with combination therapy compared to ezetimibe (49.9 vs 18.1%; P<0.001). Combination therapy (simvastatin 10 mg) and simvastatin 80 mg produced a 44% reduction in LDL-C at 12 weeks (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo			from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP	Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks, compared to the next highest dose of simvastatin (P<0.01). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C and apo B at 12 weeks compared to simvastatin (P<0.01 for all). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to simvastatin (P=0.03). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non–HDL-C and apo B at 12 weeks compared to ezetimibe (P<0.01 for all). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to ezetimibe (P=0.02). A significantly greater proportion of patients receiving combination therapy experienced a reduction in LDL-C >50% from baseline compared to simvastatin (P value not reported). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups (72 vs 69%, respectively; P value not reported).
Goldberg et al.[62] (2004) Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs	DB, MC, RCT Patients ≥18 years of age with primary hypercholesterolemia, ALT and AST ≤2 times the upper limit of normal, no active	N=887 20 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in	Primary: Averaged across all doses, combination therapy was associated with a significant 14.8% reduction in LDL-C at 12 weeks compared to simvastatin (53.2 vs 38.5%; P<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	liver disease, CK ≤1.5 times the upper limit of normal		TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP; proportion of patients reaching their NCEP ATP III LDL-C goal <130 or <100 mg/dL at 12 weeks	12 weeks compared to the next highest dose of simvastatin (P<0.001). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130 or <100 mg/dL at 12 weeks compared to simvastatin (92 and 82% vs 82 and 43%, respectively; P<0.001). Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (P=0.53). Treatment-related adverse effects were similar in the pooled simvastatin and combination therapy groups, but were more frequent than with ezetimibe and placebo (13, 14, 9 and 9%, respectively; P values not reported).
Brown et al.[63] (2001) HATS Niacin SR (Slo-Niacin®) titrated to 1 g BID and simvastatin vs antioxidants vs niacin SR (Slo-Niacin®) titrated to 1 g BID, simvastatin, and antioxidants	DB, PC Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) and with ≥3 stenoses of ≥30% of the luminal diameter or 1 stenosis of ≥50%, low HDL-C, normal LDL-C	N=160 3 years	Primary: Changes in lipid profile, arteriographic evidence of change in coronary stenosis (% stenosis caused by most severe lesion in each of nine proximal coronary segments), occurrence of first cardiovascular event (death from coronary	Primary: The mean levels of LDL-C, HDL-C, and TG were significantly changed by -42% (P<0.001), 26% (P<0.001) and -36% (P<0.001), respectively, in the niacin plus simvastatin group but were unaltered in the antioxidant only and placebo groups. Similar changes were observed when antioxidants were added to niacin plus simvastatin. The protective increase in HDL_2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (65%) was attenuated by concurrent therapy with antioxidants (28%; P=0.02). The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (P=0.16 compared to placebo) and 0.7% with niacin plus simvastatin plus antioxidants (P=0.004), and regressed by 0.4% with niacin plus simvastatin (P<0.001). The frequency of the composite primary end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebos, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary end point was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.			causes, MI, stroke or re-vascularization) Secondary: Mean change in % stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions and all lesions	90% lower in the niacin plus simvastatin group than placebo (P=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group. Secondary: In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenoses and were supported by the results for the mean minimal luminal diameter.
Zhao et al.[64] (2004) Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose) vs antioxidants (vitamin E 800 IU/day, vitamin C 1,000 mg/day, beta carotene 25 mg/day and selenium 100 µg/day) vs	ES Patients with clinical CAD (previous MI, coronary interventions or confirmed angina) including 25 with diabetes with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL	N=160 38 months	Primary: Side effects, response to the question “Overall, how difficult is it to take the study medication?” Secondary: Not reported	Primary: Patients receiving niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo; any degree of flushing (30 vs 23%; P value not significant), symptoms of fatigue, nausea and/or muscle aches (9 vs 5%; P value not significant), AST at least three times the upper limit of normal (3 vs 1%; P value not significant), CPK at least two times the upper limit of normal (3 vs 4%; P value not significant), new onset of uric acid ≥7.5 mg/dL (18 vs 15%; P value not significant) and homocysteine ≥15 µmol/L (9 vs 4%; P value not significant). There were no side effects attributable to the antioxidant regimen. Glycemic control among diabetics declined mildly with niacin plus simvastatin, but returned to pre-treatment levels at month eight and remained stable for the rest of the trial. Niacin plus simvastatin was repeatedly described by 91% of treated patients vs 86% of placebo subjects as “very easy” or “fairly easy” to take. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
niacin plus simvastatin plus antioxidants vs placebo				
Stalenhoef et al.[65] (2005) COMET Rosuvastatin 10 mg/day for 6 weeks, titrated up to rosuvastatin 20 mg/day for 6 weeks vs atorvastatin 10 mg/day for 6 weeks, titrated up to atorvastatin 20 mg/day for 6 weeks vs placebo daily for 6 weeks, followed with rosuvastatin 20 mg/day for 6 weeks	DB, DD, PG, RCT Patients ≥18 years of age with metabolic syndrome, LDL-C ≥3.36 mmol/L and 10 year CHD risk score of >10%	N=401 12 weeks	Primary: Percentage change from baseline in LDL-C at six weeks Secondary: Percentage changes from baseline in TC, LDL-C, HDL-C, non-HDL-C at 12 weeks	Primary: After six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 mg (41.7 vs 35.7%, respectively; P<0.001) and placebo (42.7 vs 0.3%, respectively; P<0.001). Secondary: After 12 weeks, rosuvastatin 20 mg was associated with a significant reduction in LDL-C compared to atorvastatin 20 mg (48.9 vs 42.5%, respectively; P<0.001). After six and 12 weeks, rosuvastatin was associated with significantly greater improvements in TC (P<0.001), HDL-C (P<0.01) and non-HDL-C (P<0.001) compared to atorvastatin.
Constance et al.[66] (2007)	DB, MC, PG, RCT	N=661	Primary: Change from	Primary: Across all doses, combination therapy was associated with a significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 20 mg/day vs ezetimibe 10 mg/day plus simvastatin 20 or 40 mg/day All patients received atorvastatin 10 mg/day during a 4 week run in period.	Patients ≥18 years of age, with type 2 diabetes, HbA_{1c} ≤10.0%, ALT/AST levels <1.5 times the upper limit of normal and CK <1.5 times the upper limit of normal	6 weeks	baseline in LDL-C Secondary: Changes from baseline in TC, HDL-C, TG, non-HDL-C, apo B, LDL-C:HDL-C and TC:HDL-C	reduction in LDL-C compared to atorvastatin (P≤0.001). Secondary: Across all doses, combination therapy was associated with significant reductions in TC, non-HDL, apo B, LDL-C:HDL-C and TC:HDL-C compared to atorvastatin (P≤0.001 for all). Combination therapy (simvastatin 40 mg) was associated with a significant reduction in hsCRP compared to atorvastatin (P=0.006). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <2.5 mmol/L compared to atorvastatin (90.5 [10-20 mg], 87.0 [10-40 mg] and 70.4%, respectively; P≤0.001). The incidence of drug-related adverse effects was similar with combination therapy and atorvastatin (0.5 [10-20 mg], 0.5 [10-40 mg] and 2.3%, respectively; P value not reported).
Kumar et al.[67] (2009) Ezetimibe 10 mg/day plus fenofibrate 160 mg/day vs atorvastatin 10 mg/day	RCT, XO Patients with hypercholesterolemia requiring pharmacotherapy	N=43 12 weeks	Primary: Percentage reduction of LDL-C Secondary: Percent changes from baseline in TC, HDL-C and TG	Primary: LDL-C decreased by 34.6 vs 36.7% with combination therapy and atorvastatin (P=0.46). Secondary: Both treatments provided similar improvements in TC (-25.1 vs -24.6%; P=0.806) and HDL-C (10.1 vs 8.9%; P=0.778). Combination therapy showed a trend towards a greater reduction in TGs (25.4 vs 14.5%; P=0.079), although there were no significant difference between the two treatments in terms of the improvement in TC:HDL-C (-29.0 vs -28.7%; P=0.904).
Goldberg et al.[68] (2009) Fenofibric acid 135 mg/day vs	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (fasting TG ≥150 mg/dL, HDL-C	N=613 12 weeks	Primary: Percent changes from baseline in TG, HDL-C and LDL-C Secondary: Percent changes	Primary: Combination therapy (atorvastatin 20 mg) resulted in significantly greater improvements in TG (-45.6 vs -16.5%; P<0.001) and HDL-C (14.0 vs 6.3%; P=0.005) compared to atorvastatin 20 mg and LDL-C (-33.7 vs -3.4%; P<0.001) compared to fenofibric acid. Similarly, significantly greater improvements were observed with combination therapy (40 mg) in TG (-42.1 vs -23.2%; P<0.001) and HDL-C (12.6 vs 5.3%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 20, 40 or 80 mg/day vs fenofibric acid 135 mg/day plus atorvastatin 20 or 40 mg/day	<40 mg/dL for men and <50 mg/dL for women and LDL-C ≥130 mg/dL after lipid therapy washout)		from baseline in VLDL-C, TC, apo B and hsCRP; safety	P=0.010) compared to atorvastatin 40 mg and LDL-C (-35.4 vs -3.4%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (20 mg) resulted in significantly higher mean percentages of decrease in non-HDL-C compared to fenofibric acid (P=0.026) and in VLDL-C compared to atorvastatin 20 mg (P=0.046). Combination therapy (40 mg) also resulted in significantly higher mean percentage of decrease in non-HDL-C compared to fenofibric acid (P<0.001) and in VLDL-C compared to atorvastatin 40 mg (P<0.001). Improvements in other secondary variables were similar between combination therapy and atorvastatin (TC; P=0.688, apo B; P=0.688 and hsCRP; P=0.074).
Bays et al.[69] (2003) ADVOCATE Niacin ER-lovastatin 1,000-40 mg/day vs niacin ER-lovastatin 2,000-40 mg/day vs simvastatin 40 mg/day vs atorvastatin 40 mg/day	MC, OL, RCT Patients 18 to 70 years of age with 2 consecutive LDL-C ≥160 (if no CAD) or ≥130 mg/dL (with CAD), TG <300 mg/dL and HDL-C <45 (men) or <50 mg/dL (women)	N=315 16 weeks	Primary: Percent change from baseline in LDL-C and HDL-C Secondary: Percent change from baseline in TC, apo B, apo AI, and HDL_2-C and HDL_3-C; median percent change in TG and Lp(a)	Primary: Atorvastatin was associated with a significant 49% reduction in LDL-C compared to a 39, 42 and 39% reduction observed with niacin ER-lovastatin 1,000-40 mg, niacin ER-lovastatin 2,000-40 mg and simvastatin, respectively (P≤0.05 for all). Combination therapy was associated with a significant increase in HDL-C compared to atorvastatin and simvastatin (17, 32, 6 and 7%, respectively; P≤0.05 for all). Secondary: Combination therapy and atorvastatin were associated with significant reductions in TG compared to simvastatin (29, 49, 31 and 19%, respectively; P≤0.05 for all). Combination therapy was associated with a significant reduction in Lp(a) compared to atorvastatin and simvastatin (19, 21, 0 and 2%, respectively; P≤0.05 for all). Combination therapy and simvastatin were associated with significant increases in apo AI compared to atorvastatin (7, 14, 6 and 2%, respectively; P<0.05 for all). Combination therapy (2,000/40 mg) and atorvastatin were associated with significant reductions in apo B compared to combination therapy (2,000/40

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				mg) and simvastatin (38, 40, 33 and 31%, respectively; P<0.05). Combination therapy was associated with a significant increase in HDL_2-C and HDL_3-C compared to atorvastatin and simvastatin (P<0.05).
Sansanayudh et al.[70] (2010) Pitavastatin 1 mg QD vs atorvastatin 10 mg QD	OL, PG, RCT Patients ≥18 years of age with hypercholesterolemia who had an indication for statin therapy according to the NCEP ATP III guidelines	N=100 8 weeks	Primary: Change from baseline in serum lipid levels Secondary: Proportion of patients who achieved NCEP ATP III LDL-C goal, safety, monthly cost per percent of LDL-C reduction	Primary: Both treatments achieved significant reductions in TC and LDL-C (P<0.05). The percentages of reduction in TC and LDL-C with pitavastatin was significantly less compared to atorvastatin (27.55 vs 32.31%; P=0.005 and 37.37 vs 45.75%; P<0.001). Pitavastatin was associated with significant reductions in TG (P=0.001), while atorvastatin was not (P=0.062); however, the changes between the two treatments were not different (P=0.661). Changes in HDL-C were also not significantly different between the two treatments (P=0.294). Secondary: Overall, 79% of all patients achieved their LDL-C goal and there was no significant difference between the two treatments (74 vs 84%; P=0.220). In the high risk category (LDL-C goal <100 mg/dL), there was no difference in the proportion of patients who achieved their LDL-C goal (42.86 vs 71.43%; P=0.127). The possible adverse events of pitavastatin vs atorvastatin included muscle pain (five vs two patients), vertigo (two vs two patients), nausea (three vs one patients), vomiting (one vs one patient), headache (one vs one patient), muscle weakness (one vs zero patients) and stomach ache (zero vs one patients) (P>0.05). During the trial, two patients receiving pitavastatin withdrew from treatment due to an adverse event.
Gumprecht et al.[71] (2011) Atorvastatin 20 mg/day vs pitavastatin 4 mg/day	AC, DB, DD, MC, NI Patients 18 to 75 with type 2 diabetes mellitus (hemoglobin HbA_{1c} ≤7.5% and combined dyslipidemia and	N=418 56 weeks (12 weeks DB, 44 weeks OL extension)	Primary: Change in LDL-C at 12 weeks, proportion of patients achieving LDL-C targets at weeks 16 and 44 and safety	Primary: The mean percent change in LDL-C at week 12 was -40.8% for pitavastatin and -43.3% for atorvastatin. The NI analysis of changes in LDL-C at the week 12 did not fulfill the predefined NI criterion since the mean treatment difference for pitavastatin 4 mg compared to atorvastatin 20 mg was -2.33%, outside the lower bound of the 95% CI (-6.18%). A high proportion of patients in the pitavastatin and atorvastatin groups achieved lipid targets during long-term treatment (percentages not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	TG despite diet modification and oral antidiabetic treatment or insulin		and tolerability at 56 weeks Secondary: TC, HDL-C, TG, TC/HDL-C ratio, non-HDL-C, non-HDL-C/HDL-C ratio, apo B, apo AI, apo B: apo AI ratio, hs-CRP, adiponectin LDL, remnant-like particle cholesterol, oxidized LDL and safety	Most adverse events were mild or moderate in severity with few discontinuations due to treatment-related adverse events (2.5 and 3.6% for pitavastatin and atorvastatin in the core study, and 2.1 and 1.4%, respectively, in the extension study). One patient in the pitavastatin group died of a MI during the study, which was not considered to be related to the study drug. The most common adverse events considered to be treatment related were nasopharyngitis and myalgia. The incidence of myalgia during the extension study was slightly lower in the pitavastatin group than in the atorvastatin group (4.2 vs 7.0%, respectively). The incidence of clinically significant elevation of liver enzymes was low in both groups in both the core and extension studies. During the core study, mean blood glucose levels in the pitavastatin group showed a non-significant increase of 2.1% from baseline to week 12. By contrast, mean blood glucose in the atorvastatin group increased significantly from baseline to week 12 by 7.2% (P<0.05). Secondary: Mean TC, TG and non-HDL-C levels decreased from baseline in both the core study and the end of the extension study to a similar degree in both groups. There were no notable between-treatment differences in the observed effects on other lipid parameters such as TC/HDL-C ratio, non-HDL-C/HDL-C ratio and apo B. Pitavastatin and atorvastatin were similar in their effect on increasing HDL-C. By the end of the extension study, more patients receiving pitavastatin had increased their HDL-C levels. Pitavastatin and atorvastatin treatment also reduced CRP, oxidized LDL and increased levels of adiponectin to similar extents.
Yoshitomi et al.[72] (2006) Pitavastatin 1 mg QD vs	MC, OL Patients ≥18 years of age with hypercholesterolemia (LDL >140 mg/dL and TG	N=137 12 weeks	Primary: Mean percent reductions from baseline in TC, LDL-C, HDL-C and TG	Primary: There were no significant differences between the two treatments in reducing baseline TC (28±8 vs 29±10%) and LDL-C (38±13 vs 41±12%) (P values not reported). There were no differences between the two treatments in increasing baseline HDL-C (3±12 vs 7±12%; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 10 mg QD	<400 mg/dL) treated with or without lipid lowering agents		Secondary: Safety	Atorvastatin achieved a significantly greater mean percent reduction from baseline in TG compared to pitavastatin (21±25 vs 11±30%; P<0.05). Secondary: Treatment with both pitavastatin and atorvastatin was well tolerated. No serious adverse event was associated with the treatment. No adverse events of musculoskeletal, renal or hepatocellular toxicity occurred and no patient had an elevation of the CK level that was >3 times the upper limit of normal.
Lee et al.[73] (2007) Pitavastatin 2 mg QD vs atorvastatin 10 mg QD Patients who did not achieve the LDL-C goal by week 4 received a double dose of the assigned medications for an additional 4 weeks.	MC, OL, RCT Patients 20 to 79 years of age with untreated hypercholesterolemia, fasting TG <400 mg/dL and a LDL-C >130 mg/dL after a 4 week dietary lead in period	N=268 8 weeks	Primary: Changes from baseline in lipid parameters and hsCRP Secondary: Tolerability	Nine (8.2%) patients receiving pitavastatin and 12 (10.7%) patients receiving atorvastatin did not achieve the LDL-C goal by week four and received a double dose of their assigned medication for the remaining four weeks. Primary: There was no significant difference between the two treatments in the proportion of patients achieving the LDL-C goal at eight weeks (92.7 vs 92.0%; P value not reported). There was no difference between the two treatments in terms of the mean percent changes in LDL-C (-42.9 vs -44.1%), TC (-28.0 vs -29.6%), TG (-9.9 vs -11.0%), HDL-C (7.1 vs 6.7%) and hsCRP (-23.9 vs -15.4%) (P values not reported). Secondary: Both treatments were well tolerated and 21 adverse reactions considered related to study medication occurred in 14 patients receiving pitavastatin and 23 occurred in 19 patients receiving atorvastatin. There were no clinically relevant changes in laboratory values.
Sasaki et al.[74] (2008) Pitavastatin 2 mg QD	MC, OL, PG, RCT Patients ≥20 years of age with LDL-C ≥140 mg/dL,	N=189 52 weeks	Primary: Percent change from baseline in serum HDL-C Secondary:	Primary: Pitavastatin was associated with an increase in HDL-C of 8.2%, which was significantly greater than atorvastatin (2.9%; P=0.031). Secondary: Atorvastatin was associated with significant reductions LDL-C (-40.1 vs -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 10 mg QD	HDL-C <80 mg/dL, TG <500 mg/dL and glucose intolerance		Percent change from baseline in LDL-C, non-HDL-C, LDL-C:HDL-C, TG, apo AI, apo B, apo B:AI and apo E; tolerability	33.0%; P=0.002), non-HDL-C (-37.4 vs -31.1%; P=0.004), apo B (-35.1 vs -28.2%; P<0.001) and apo E (-28.1 vs -17.8%; P<0.001) compared to pitavastatin. There were no differences between the two treatments in terms of changes in LDL-C:HDL-C, apo B:AI and TG. Apo AI increased significantly more with pitavastatin compared to atorvastatin (5.1 vs 0.6%; P=0.019). Effects on glucose metabolism were similar between the two treatments, measured by fasting plasma insulin, FPG and HbA_{1c}. Initiation of medication use for the treatment of diabetes occurred at a similar rate with both treatments (11%). Adverse events occurred at a similar rate between the two treatments.
Saito et al.[75] (2002) Pitavastatin 2 mg/day vs pravastatin 10 mg/day	DB, MC, PG, RCT Patients 20 to 75 years of age with primary hyperlipidemia (TC ≥200 mg/dL and TG <400 mg/dL)	N=240 12 weeks	Primary: Mean percent changes from baseline in TC, LDL-C and TG Secondary: Mean percent changes from baseline in apo B, apo CII, apo CIII and apo E; safety	Primary: Pitavastatin achieved significantly greater mean percent reductions from baseline in TC and LDL-C (28.2 and 37.6%) compared to pravastatin (14.0 and 18.4%; both P<0.001). In cases of a baseline TG level ≥150 mg/dL, the mean percent reduction of TG with pitavastatin (23.3%) showed non-inferiority to that observed with pravastatin (20.2%; P=0.024). Secondary: Mean percent reductions in apo B, apo CII, apo CIII and apo E with pitavastatin (33.8, 15.7, 9.5 and 22.9%) were significantly greater compared to pravastatin (16.9, 6.1, 2.6 and 12.6%; P values not reported). The adverse event profile was similar for both treatments and neither treatment caused clinically relevant laboratory abnormalities. Three patients receiving pitavastatin and two patients receiving pravastatin withdrew from the study due to adverse events considered to be drug-related.
Park et al.[76] (2005) Pitavastatin 2 mg QD	MC, OL, Phase III, PRO, RCT Patients 20 to 75 years of age with	N=104 8 weeks	Primary: Mean percent change from baseline in LDL-C	Primary: There was no significant difference between the two treatments in the reduction in LDL-C (11.6 vs 12.9%; P=0.648). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs simvastatin 20 mg QD	hypercholesterolemia, fasting TG <600 mg/dL and LDL-C >130 mg/dL after a 4 week dietary lead in period		Secondary: Mean percent change from baseline in TC, TG and HDL-C; safety	There were no significant differences between the two treatments in the changes in TC (-8.9 vs -8.7%; P=0.405), TG (-20.6 vs 36.9%; P=0.147), or HDL-C (13.4 vs 16.2%; P=0.127). No serious adverse events were observed in either treatment. One patient receiving pitavastatin and four patients receiving simvastatin had to discontinue the study medication due to adverse events. Elevations in CK greater than two times upper limit of normal were observed in 3.8 and 9.8% of pitavastatin- and atorvastatin-treated patients (P=0.269). Mild elevations in AST less than two fold times upper limit of normal was observed in one patient receiving simvastatin.
Ose L et al.[77] (2009) Pitavastatin 2 or 4 mg/day vs simvastatin 20 or 40 mg/day	AC, DB, DD, PRO, RCT Patients diagnosed with either primary hypercholesterolemia or combined dyslipidemia	N=857 12 weeks	Primary: Changes in lipid panel Secondary: Safety profiles	Primary: Pitavastatin 2 mg was associated with a significant improvement in LDL-C, non-HDL-C and TC compared to simvastatin 20 mg (P=0.014, 0.021 and 0.041 respectively). LDL-C was reduced by 39% with pitavastatin 2 mg compared to 35% with simvastatin 20 mg. Pitavastatin 4 mg and simvastatin 40 mg had similar effects on the lipid panel. Reductions in LDL-C were 44% with pitavastatin 4 mg and 43% for simvastatin 40 mg. Secondary: Safety profiles were similar at all dose levels.
Eriksson et al.[78] (2011) Pitavastatin 4 mg/day vs simvastatin 40 mg/day	AC, DB, DD, MC, NI, PG, RCT Patients 18 to 75 years of age with primary hypercholesterolemia or combined dyslipidemia that was uncontrolled (LDL-C ≥130 mg/dL and ≤5,220 mg/dL; TG ≤400 mg/dL)	N=355 12 weeks	Primary: Percentage change in LDL-C from baseline Secondary: Proportion of patients reaching LDL-C targets, percentage changes from baseline in concentrations	Primary: The mean LDL-C concentrations decreased from baseline by -44.0% with pitavastatin compared to -43.8% with simvastatin. The adjusted mean treatment difference was 0.31%, which was within the predefined limits of NI (95% CI, -2.47 to 3.09; P=0.829). Secondary: There was no statistically significant difference in the proportion of patients achieving NCEP LDL-C targets (87.1 vs 85.6%; P=0.695) or EAS LDL-C targets (87.1 vs 81.4%; P=0.170) between patients treated with pitavastatin or simvastatin. Pitavastatin provided a significantly greater reduction in triglycerides compared to simvastatin (-19.8 vs -14.8%; P=0.044), as well as a greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	despite dietary measures, and at least two cardiovascular risk factors		of TG, TC, HDL-C, non-HDL-C, apo B and apo AI, and absolute changes from baseline in concentrations of oxidized LDL, CRP and ratios of TC:HDL-C, non-HDL:HDL-C, and apo B/apo A1 and safety	increase in HDL-C with pitavastatin (6.8 vs 4.5%), which was not statistically significant (P=0.083). There were no other significant differences in secondary lipid measures between the two groups. Treatment-emergent adverse events occurred in 51.1% of patients receiving pitavastatin and 50.4% of patients receiving simvastatin. The most commonly reported treatment-emergent adverse events were headache, nasopharyngitis, constipation, myalgia and back pain.
Rosenson et al.[79] (2009) Rosuvastatin 10 mg QD for 6 weeks, followed by 20 mg thereafter vs atorvastatin 10 mg QD for 6 weeks, followed by 20 mg thereafter vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with the metabolic syndrome, LDL-C 130 to 250 mg/dL and a 10-year CHD risk score >10%	N=318 12 weeks	Primary: Lipoprotein particle concentrations Secondary: Not reported	Primary: After six weeks of therapy, rosuvastatin 10 mg and atorvastatin 10 mg significantly reduced LDL-C, LDL particle concentration, apo B, and non-HDL-C compared to placebo (P<0.001). Rosuvastatin significantly reduced LDL-C (P<0.001), LDL particle concentration (P<0.05), and non-HDL-C (P<0.01) compared to atorvastatin after six and 12 weeks. After six weeks of therapy, rosuvastatin 10 mg and atorvastatin 10 mg significantly reduced VLDL particle concentration and serum triglycerides compared to placebo (P<0.001). There was no difference between the two statins on either end point at week 6 or 12. After six weeks of therapy, rosuvastatin 10 mg increased HDL particle concentration (15%) and HDL-C (10%) compared to placebo (P<0.001). Atorvastatin significantly increased HDL particle concentration compared to placebo (6%, P=0.013); however, there was no difference in HDL-C (4%, P=0.45). Rosuvastatin significantly increased HDL particle concentration and HDL-C compared to atorvastatin after six and 12 weeks (P≤0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Neither statin showed a significant effect on apo AI compared to placebo; however, increases in apo AI were significantly greater with rosuvastatin than atorvastatin at six and 12 weeks (P=0.001 and P=0.02, respectively). A higher proportion of patients receiving rosuvastatin achieved LDL-C <100 mg/dL compared to atorvastatin at six and 12 weeks (P<0.01 and P<0.0001, respectively). Patients receiving rosuvastatin achieved LDL particle concentration <1,300 nmol/L at 12 weeks (P=0.02) and <1,000 nmol/L at six weeks (P=0.02) compared to atorvastatin. The percentage of patients who attained LDL particle concentration <1,300 nmol/L was similar to that achieving LDL-C <100 mg/dL. Secondary: Not reported
Park et al.[80] (2010) Rosuvastatin 10 mg/day vs atorvastatin 10 mg/day	MC, OL, PG Patients ≥18 years of age with nondiabetic metabolic syndrome and hypercholesterolemia	N=351 6 weeks	Primary: Percent change from baseline in TC, LDL-C, HDL-C, TG, non-HDL-C, apo AI and apo B; proportion of patients achieving NCEP ATP III LDL-C goals (<100, <130 and <160 mg/dL); change from baseline in metabolic parameters; safety Secondary:	Primary: After six weeks, significantly greater reductions in TC (35.94±11.38 vs 30.07±10.46%; P<0.001), LDL-C (48.04±14.45 vs 39.52±14.42%; P<0.001), non-HDL-C (42.93±13.15 vs 35.52±11.76%; P<0.001) and apo B (38.7±18.85 vs 32.57±17.56%; P=0.002) were achieved with rosuvastatin compared to atorvastatin. No differences between treatments were observed in changes in HDL-C (P=0.448), TG (P=0.397) and apo AI (P=0.756). Overall, the proportion of patients achieving the LDL-C goals was significantly greater with rosuvastatin compared to atorvastatin (87.64 vs 69.88%; P<0.001). Corresponding proportions for the LDL-C goals <100, <130 and <160 mg/dL were: 82.7 vs 59.2 (P<0.001), 94.3 vs 84.2 (P=0.032) and 96.8 vs 97.3% (P=0.990). Changes in glucose (P=0.231), insulin (P=0.992), HbA_{1c} (P=0.456) and HOMA index (P=0.910) were not significantly different between the two treatments. The safety and tolerability of the two treatments were similar.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			Not reported	Secondary: Not reported
Mazza et al.[81] (2008) Rosuvastatin 10 mg QD vs atorvastatin 20 mg QD	OL, RCT Patients 18 to 65 years of age with primary hypercholesterolemia (LDL-C >200 mg/dL) and at high risk for CHD	N=106 48 weeks	Primary: Plasma levels of TC, TG, LDL-C HDL-C, non-HDL-C Secondary: Not reported	Primary: After 48 weeks of treatment, atorvastatin significantly lowered TC, LDL-C, and non HDL-C levels (-21.6; -30; -26.98%, respectively; P<0.001 combined). HDL-C levels increased 4.52% (P value not significant) TG levels decreased 4.62% (P value not significant). After 48 weeks of treatment, rosuvastatin significantly lowered TC, LDL-C, non HDL-C, and TG levels (-35.77, -44.32, -43.12, -36.41%, respectively; P<0.001 combined). HDL-C level also decreased -2.04% (P value not significant). Rosuvastatin was more effective than atorvastatin in reducing plasma levels of TC, LDL-C, non-HDL-C and TG (-35.77, -44.32, -43.12, -36.41%, respectively, with rosuvastatin vs -21.62, -30, -26.98, -4.62%, respectively, with atorvastatin; P<0.005). Both drugs had no significant effect on plasma HDL-C levels relative to baseline. There were no significant differences in either treatment group in parameters related to safety. Secondary: Not reported
Betteridge et al.[82] (2007) ANDROMEDA Rosuvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks vs	DB, MC, PG, RCT Patients ≥18 years of age with type 2 diabetes, ≥2 FPG levels of ≥7 mmol/L and TG ≤6 mmol/L	N=509 16 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Percentage changes from baseline in LDL-C, TC, HDL-C, TG,	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (57.4 vs 46.0%; P=0.001). Secondary: Rosuvastatin was associated with a significant reduction in apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C and apo B compared to atorvastatin (P<0.001). Rosuvastatin was associated with a significant reduction in HbA_{1c} compared to atorvastatin (P=0.049).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks All patients were randomized after a 4 week dietary lead in period.			non-HDL-C, cholesterol ratios, apo B, apo ratio and HbA_{1c}; proportion of patients achieving 2003 Joint European Societies LDL-C (<2.5 mmol/L) and TC (<4.5 mmol/L) goals	A significantly greater proportion of patients receiving rosuvastatin achieved LDL-C goals compared to patients receiving atorvastatin (95.6 vs 87.3%; P=0.002). A significantly greater proportion of patients receiving rosuvastatin achieved TC goals compared to patients receiving atorvastatin (93.4 vs 86.0%; P=0.01).
Betteridge et al.[83] (2007) ANDROMEDA Rosuvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks vs atorvastatin 10 mg/day for 8 weeks, titrated up to 20 mg/day for 8 weeks All patients were randomized after a 4 week dietary lead in period.	Subanalysis of ANDROMEDA Patients ≥18 years of age with type 2 diabetes, ≥2 FPG levels of ≥7 mmol/L and TG of ≤6 mmol/L	N=509 16 weeks	Primary: Composite of changes from baseline in hsCRP <2 mg/L and LDL-C <70 mg/dL Secondary: Not reported	Primary: Rosuvastatin was associated with a significant reduction in the primary endpoint compared to atorvastatin (58 vs 37%; P<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Clearfield et al.[84] (2006) PULSAR Rosuvastatin 10 mg QD vs atorvastatin 20 mg QD	MC, OL, PG, RCT Patients ≥18 years of age with hypercholesterolemia and either a history of CHD or a CHD risk equivalent, with the mean of the 2 most recent LDL-C (within 15% of each other) ≥130 to <220 mg/dL, as well as TG <400 mg/dL	N=996 6 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving the NCEP ATP III and the 2003 European LDL-C goals (<100 mg/dL), the 2003 European LDL-C goal for patients at greatest risk, the NCEP ATP III non-HDL-C goal (<130 mg/dL), combined LDL-C:TC goal <175 to 190 mg/dL; percentage changes from baseline in HDL-C, TC, TG, non-HDL-C, apo B, LDL-C:HDL-C, TC:HDL-C, non-HDL-	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (42.7 vs 44.6%; P<0.05). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved NCEP ATP III and the 2003 European LDL-C goals compared to patients receiving atorvastatin (68 vs 63%; P<0.05). In addition, a significantly greater proportion of high risk CHD patients receiving rosuvastatin achieved the 2003 European LDL-C goals compared to high risk CHD patients receiving atorvastatin (65.6 vs 60.3%; P>0.05). A nonsignificant greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III non-HDL-C goal compared to patients receiving atorvastatin (69.7 vs 65.0%; P>0.05). A nonsignificant greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III combined LDL-C:TC goal compared to atorvastatin (55.2 vs 53.3%; P>0.05). Rosuvastatin was associated with a significant increase in HDL-C compared to atorvastatin (6.4 vs 3.1%; P<0.001). There was no difference in the changes of TC, TG, non-HDL-C and apo B observed with rosuvastatin and atorvastatin (P>0.05). Rosuvastatin was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin (47.6 vs 44.0%; P<0.001). Rosuvastatin was associated with a significant reduction in TC:HDL-C compared to atorvastatin (34.6 vs 32.3%; P<0.01). Rosuvastatin was associated with a significant reduction in non-HDL-C:HDL-C compared to atorvastatin (43.3 vs 40.2%; P<0.001). Atorvastatin was associated with a significant increase in Lp(a) compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			C:HDL-C and Lp(a); safety	rosuvastatin (13.3 vs 2.1%; P<0.001). The frequency and type of adverse events were similar with both treatments (27.5 vs 26.1%; P value not reported). The most commonly reported adverse effects were myalgia and urinary tract infections.
Deedwania et al.[85] (2007) IRIS Rosuvastatin 10 or 20 mg/day vs atorvastatin 10 or 20 mg/day All patients were randomized after a 6 week dietary lead in period.	MC, OL, RCT South-Asian patients ≥18 years of age with CHD or CHD risk equivalent and LDL-C ≥100 mg/dL or ≥2 risk factors, 10 year CHD risk 10 to 20% and LDL-C ≥130 mg/dL or 0 to 1 risk factor and LDL-C ≥160 mg/dL, with TG <500 mg/dL	N=740 6 weeks	Primary: Percentage change from baseline in LDL-C Secondary: Proportion of patients achieving NCEP ATP III LDL-C goals; percentage change from baseline in non-HDL-C, HDL-C, TC and TG; safety	Primary: At six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 mg (P=0.0023). The difference in LDL-C reduction from baseline at six weeks between rosuvastatin 20 mg and atorvastatin 20 mg was not significant (P value not reported). Secondary: The proportion of patients achieving NCEP ATP III LDL-C goals was similar with rosuvastatin 10 and 20 mg and atorvastatin 10 and 20 mg (79, 89, 76 and 85%, respectively; P value not reported). At six weeks, rosuvastatin 10 mg was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin 10 mg (P<0.017). There were no clinically relevant differences between treatments in adverse events or incidence of CK >10 times the upper limit of normal, ALT >3 times the upper limit of normal, proteinuria or hematuria.
Ferdinand et al.[86] (2006) ARIES Rosuvastatin 10 or 20 mg QD vs atorvastatin 10 or 20 mg QD All patients were randomized after	OL, RCT African American patients ≥18 years of age with LDL ≥160 to ≤300 mg/dL, TG <400 mg/dL	N=774 6 weeks	Primary: The change from baseline in LDL-C Secondary: Changes from baseline in other lipid parameters	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (P<0.017). Secondary: Rosuvastatin was associated with a significant reduction in TC, non-HDL-C, apo B and lipoprotein and apo ratios compared to atorvastatin (P<0.017). Rosuvastatin was associated with a significant increase in HDL-C compared to atorvastatin (P<0.017). Adverse events were similar with rosuvastatin and atorvastatin (34.4 and 33.6%, respectively; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
a 6 week dietary lead in period.				
Lloret et al.[87] (2006) STARSHIP Rosuvastatin 10 or 20 mg QD vs atorvastatin 10 or 20 mg QD All patients were randomized after a 6 week dietary lead in period.	MC, OL, RCT Hispanic American patients ≥18 years of age with a 10 year risk >10% for CHD, current CHD or its equivalent, LDL ≥130 to ≤300 mg/dL on 2 measurements within 15% of each other, TG <400 mg/dL	N=696 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Proportion of patients achieving NCEP ATP III lipid goals; percent change from baseline in TC, apo B, non-HDL-C, TG, HDL, apo AI, LDL-C:HDL-C, TC:HDL-C and apo B:apo AI; safety	Primary: Rosuvastatin 10 and 20 mg was associated with a significant reduction in LDL-C compared to atorvastatin 10 and 20 mg (45, 50, 36 and 42%, respectively; P<0.0001). Secondary: A greater proportion of patients receiving rosuvastatin 10 and 20 mg achieved LDL-C goals compared to atorvastatin 10 and 20 mg (78, 88, 60 and 73%, respectively; P value not reported). Rosuvastatin 10 and 20 mg was associated with a significant reduction in TC compared to atorvastatin 10 and 20 mg (10 mg; P<0.0001, 20 mg; P<0.01, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in apo B compared to atorvastatin 10 and 20 mg (10 mg; P<0.0001, and 20 mg; P<0.017, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in LDL-C:HDL-C compared to atorvastatin 10 and 20 mg, respectively, at six months (P<0.0001 for both, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in TC:HDL-C compared to atorvastatin 10 and 20 mg (10 mg; P<0.0001, 20 mg; P<0.01, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in non-HDL-C:HDL-C compared to atorvastatin 10 and 20 mg (10 mg; P<0.0001, 20 mg; P<0.01, respectively). Rosuvastatin 10 and 20 mg was associated with a significant reduction in apo B:apo AI compared to atorvastatin 10 and 20 mg (P<0.01 for both, respectively). Adverse events were similar between treatments (P value not reported). There

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				were no cases of myopathy, rhabdomyolysis or clinically significant increases in serum CK.
Milionis et al.[88] (2006) ATOROS Rosuvastatin 10 mg QD for 6 weeks, titrated to 20 mg/day vs atorvastatin 20 mg QD for 6 weeks, titrated to 40 mg/day All patients were randomized after a 6 week dietary lead in period.	OL, PG, RCT Adult patients free of symptomatic ischemic heart disease or any other clinically evident heart disease, at moderate risk for CHD according to NCEP ATP classification, with baseline TC >240 mg/dL and TG <350 mg/dL	N=180 24 weeks	Primary: Proportion of patients achieving the NCEP ATP III LDL-C goal (<130 mg/dL) Secondary: Changes from baseline in LDL-C, HDL-C, TC, TG, non-HDL-C and apo B	Primary: After six weeks, 75.0 and 71.7% of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin and atorvastatin, respectively (P value not reported). Secondary: Both rosuvastatin and atorvastatin were associated with significant reductions in LDL-C (48.7 vs 44.6%; P<0.001). Rosuvastatin was associated with a significant five percent increase in HDL-C (P<0.001). Atorvastatin was associated with a significant 2.1% reduction in HDL-C (P<0.001). Compared to atorvastatin, rosuvastatin was associated with a significantly greater increase in HDL-C (P=0.002). Both rosuvastatin and atorvastatin were associated with significant reductions in TC (36.1 vs 36.9%; P<0.001). Both rosuvastatin and atorvastatin were associated with significant reductions in TG (29.0 vs 27.8%; P<0.001). Both rosuvastatin and atorvastatin were associated with significant reductions in non-HDL-C (45 vs 46%; P<0.001). Both rosuvastatin and atorvastatin were associated with significant reductions in apo B (29 vs 26%; P<0.001). The incidence of myalgia was similar with both treatments (3%; P value not reported). There were no reports of significant ALT or CK elevations.
Ai et al.[89] (2008) STELLAR Rosuvastatin 40 mg/day vs	OL Patients ≥18 years of age with hypercholesterolemia, LDL-C ≥160 to <250 mg/dL and TG <400	N=271 6 weeks	Primary: Changes from baseline in direct LDL-C and small dense LDL-C Secondary:	Primary: Rosuvastatin was associated with a significant reduction from baseline in direct LDL-C compared to atorvastatin (52 vs 50%; P=0.01). Rosuvastatin was associated with a significant reduction from baseline in small dense LDL-C compared to atorvastatin (53 vs 46%; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 80 mg/day	mg/dL		Percentage changes from baseline in HDL-C, TC, TG, non-HDL-C and TC:HDL-C	Rosuvastatin was associated with a significant increase from baseline in HDL-C compared to atorvastatin (10 vs 2%; P<0.001). There was no difference between treatments in TC (P=0.10) and TG (P=0.50) reductions. Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin (51 vs 48%; P<0.0078). Rosuvastatin was associated with a significant reduction in TC:HDL-C compared to atorvastatin (46 vs 39%; P<0.001).
Leiter et al.[90] (2007) POLARIS Rosuvastatin 40 mg QD vs atorvastatin 80 mg QD	DB, PG, RCT Patients 45 to 80 years of age with hypercholesterolemia and a history of CHD, clinical evidence of atherosclerosis or a 10 year Framingham CHD risk score >20%, with LDL-C ≥160 to <250 mg/dL and TG <400 mg/dL	N=871 26 weeks	Primary: The percentage change from baseline in LDL-C levels at week eight Secondary: Percentage change from baseline in LDL-C levels at week 26, percentage change from baseline in other lipids and lipoproteins at weeks eight and 26, proportion of patients achieving NCEP ATP III and 2003 European lipid goals at eight	Primary: After eight weeks, rosuvastatin was associated with a significantly greater reduction in LDL-C compared to atorvastatin (56 vs 52%; P<0.001). Secondary: After 26 weeks, rosuvastatin was associated with a significantly greater reduction in LDL-C compared to atorvastatin (57 vs 53%; P value not reported). After eight weeks, rosuvastatin was associated with a significantly greater reduction in TG (27.0 vs 22.2%; P<0.05), non-HDL-C (50.8 vs 48.3%; P<0.01), LDL-C:HDL-C (58.5 vs 53.6%; P<0.001), TC:HDL-C (44.4 vs 41.1%; P<0.001), non-HDL-C:HDL-C (53.6 vs 49.6%; P<0.001), apo B (44.6 vs 42.3%; P<0.05) and apo AI (4.2 vs -0.5%; P<0.001) compared to atorvastatin. After eight weeks, rosuvastatin was associated with a significantly greater increase in HDL-C compared to atorvastatin (9.6 vs 4.4%; P<0.001). After six weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III LDL-C goals of <100 (80 vs 72%; P<0.01) and <70 mg/dL (36 vs 18%; P<0.001) compared to patients receiving atorvastatin. After six weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the 2003 European lipid goals compared to patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			and 26 weeks, safety	receiving atorvastatin (79 vs 69%; P<0.001). The incidence of drug-related adverse events was low with both treatments (0.5 vs 0.2%; P value not reported).
Wolffenbuttel et al.[91] (2005) CORALL Rosuvastatin 10 mg QD for 6 weeks, titrated to 20 mg QD for 6 weeks, titrated to 40 mg QD for 6 weeks vs atorvastatin 20 mg QD for 6 weeks, titrated to 40 mg QD for 6 weeks, titrated to 80 mg QD for 6 weeks All patients were randomized after a 6 week dietary lead in period.	MC, OL, PG, RCT Patients ≥18 years of age with type 2 diabetes for ≥3 months, LDL ≥3.36 mmol/L in statin naïve patients or LDL 2.99 to 5 mmol/L in patients exposed to statin therapy within the previous 4 weeks, TG <4.52 mmol/L and HbA_{1c} <10.0%	N=265 24 weeks	Primary: Reduction in LDL-C, HDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B; percentage of patients who achieved LDL-C goals (<2.6 or <2.5 mmol/L) at 18 weeks Secondary: Not reported	Primary: Rosuvastatin and atorvastatin were associated with significant reductions from baseline in LDL-C, apo ratio, LDL-C:HDL-C, TC, TC:HDL-C, non-HDL-C, TG and apo B (P<0.001). Rosuvastatin was associated with significant reduction in LDL-C (P<0.01), apo ratio (P<0.05), LDL-C:HDL-C (P<0.01), TC (P<0.05), TC:HDL-C (P<0.05), non-HDL-C (P<0.05) and apo B (P<0.05) compared to atorvastatin. A significantly greater percentage of patients receiving rosuvastatin achieved LDL-C goals at 18 weeks compared to patients receiving atorvastatin (P<0.05). The incidence of treatment-related adverse events was similar between the two treatments (47 vs 50%, respectively; P value not reported). Secondary: Not reported
Bullano et al.[92] (2007) Rosuvastatin (mean daily dose, 11 mg)	RETRO Patients ≥18 years of age, initiated on rosuvastatin or atorvastatin	N=453 Up to 79 days of therapy	Primary: Percentage change from baseline in LDL-C	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin (35 vs 26%; P<0.001). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin (mean daily dose, 15 mg)	between August 1, 2003 and September 30, 2004 with ≥1 lipid level (LDL-C, TG, HDL-C, TC) obtained prior to and after therapy initiation		Secondary: Proportion of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), percentage change from baseline in HDL-C, TC, TG and non-HDL-C	NCEP ATP III LDL-C goals compared to atorvastatin, when adjusted for age, sex, LDL-lowering required to reach goal, risk category and duration of therapy (74 vs 65%; P<0.05). Unadjusted attainment rates were similar with both treatments (P=0.088). Patients receiving rosuvastatin required greater LDL-C reduction to reach their LDL-C goal compared to patients receiving atorvastatin (26.3 vs 23.5%; P<0.05). In addition, significantly more patients receiving rosuvastatin reached the updated, optional NCEP ATP III LDL-C goals compared to patients receiving atorvastatin (61 vs 48%; P<0.05). There was no difference between the two treatments in the change in HDL-C (P=0.234). Rosuvastatin was associated with a greater reduction in TC compared to atorvastatin (26 vs 20%; P<0.001). There was no difference between the two treatments in the change in TG (P=0.192). Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin (33 vs 25%; P<0.001).
Wlodarczyk et al.[93] (2008) Rosuvastatin 5, 10, 20 or 40 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day	MA (25 head-to-head RCTs) Patients with hypercholesterolemia	N=19,621 Mean 8.6 weeks (range, 4 to 12 weeks)	Primary: Change from baseline in LDL-C Secondary: Safety	Primary: At equivalent doses, rosuvastatin produced significantly larger reductions in LDL-C compared to atorvastatin (mean treatment difference, -8.52%; 95% CI, -9.23 to -7.81) or a two times higher atorvastatin dose (-3.24%; 95% CI, -4.10 to -2.38). No difference between the two treatments were observed when rosuvastatin was compared to a four times higher atorvastatin dose (1.12%; 95% CI, -0.24 to 2.48). Results were similar for DB and OL trials. The percentage of LDL-C decrease associated with rosuvastatin ranged from 41.0 to 56.0% for the 5 and 40 mg dosing regimens, respectively. Atorvastatin ranged from 37.2 to 51.3% for the 10 and 80 mg dosing regimens. Secondary: Event rates for myalgia ranged from 3.5 to 4.2% for atorvastatin 80 mg and rosuvastatin 5 mg. No clear dose-response relation was evident for either treatment and no difference between the two treatments was noted.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Rates of withdrawal were low, ranging from 4.1 to 6.4% for rosuvastatin 5 mg and atorvastatin 40 mg. Rates due to adverse events were similar between the two treatments. At the 1:1 dose ratio, the trend toward a higher rate with rosuvastatin did not reach significance (OR, 1.258; 99% CI, 0.972 to 1.627). This trend was no longer evident when only DB trials were included (OR, 0.89; 95% CI, 0.48 to 1.63). Serious adverse events tended to be lower with rosuvastatin at each dose ratio, but there was no strong evidence of a treatment effect. There were nine patients with CK >10 times the upper limit of normal and 23 deaths were reported. Rates of ALT greater than three times the upper limit of normal were highest with atorvastatin 80 mg (2.2/100 patients) and rosuvastatin 40 mg (0.8/100 patients). Within treatment MA showed that GFR tended to increase with atorvastatin and rosuvastatin by 3.8% (99% CI, 2.77 to 4.77) and 2.7% (99% CI, 1.79 to 3.58). No difference was noted between the two treatments.
Fox et al.[94] (2007) Rosuvastatin vs simvastatin	RETRO Adult patients ≥18 years of age switching to either rosuvastatin or simvastatin from another statin between August 2003 and March 2006, not receiving other antidyslipidemic medications in the 12 months before or after initiating statin therapy	N=277 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction from baseline in LDL-C Secondary: Not reported	Primary: A switch to rosuvastatin was associated with a significant reduction in LDL-C compared to a switch to simvastatin (18.5 vs 5.8%; P<0.05). A significantly greater proportion of patients who switched to rosuvastatin achieved a LDL-C reduction >25% compared to those who switched to simvastatin (44 vs 29%; P<0.05). Patients who switched from atorvastatin to rosuvastatin experienced a significantly greater reduction in LDL-C compared to those who switched to simvastatin therapy (14.6 vs 4.6%; P<0.05). Secondary: Not reported
Bullano et al.[95] (2006)	RETRO	N=8,251	Primary: Percentage	Primary: Rosuvastatin was associated with a significant reduction in LDL-C compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Rosuvastatin 5 to 40 mg/day vs other statins (atorvastatin 10 to 80 mg/day, simvastatin 5 to 80 mg/day, pravastatin 10 to 80 mg/day, lovastatin 10 to 80 mg/day and fluvastatin 20 to160 mg/day)	Patients ≥18 years of age initiated on a statin between August 1, 2003 and September 30, 2004 with ≥1 LDL-C level obtained prior to and after therapy initiation	Up to 122 days of therapy	change from baseline in LDL-C Secondary: Proportion of patients achieving the NCEP ATP III LDL-C goals (<100 mg/dL), percentage change from baseline in HDL-C, TC and TG	to other statins (33 vs 24 [atorvastatin], 20 [simvastatin], 18 [pravastatin], 13 [fluvastatin] and 16% [lovastatin]; P<0.05). Rosuvastatin 10 mg/day was associated with a significantly greater reduction in LDL-C compared to atorvastatin 10 to 20 mg/day (P<0.05) or simvastatin 10 to 20 mg/day (P<0.05). Secondary: A significantly greater proportion of patients receiving rosuvastatin achieved the NCEP ATP III LDL-C goals compared to patients receiving other statins (P<0.05). Patients receiving rosuvastatin required greater LDL-C reduction to reach their LDL-C goal compared to patients treated with other statins (29 vs 23 to 27%; P<0.05). A significantly greater proportion of patients receiving rosuvastatin achieved the updated, optional NCEP ATP III LDL-C goals compared to patients receiving other statins (58 vs 29 to 48%; P<0.05). There was no difference between rosuvastatin and other statins in HDL-C reductions (P>0.05). Rosuvastatin was associated with a significant reduction in TC compared to other statins (24% vs 18 [atorvastatin], 14 [simvastatin], 13 [pravastatin], 10 [fluvastatin] and 13% [lovastatin]; P<0.05). Rosuvastatin was associated with a significant reduction in TG compared to other statins (11% vs 6 [simvastatin], 4 [pravastatin], 4 [fluvastatin] and 5% [lovastatin]; P<0.05). There was no difference in TG reduction between rosuvastatin and atorvastatin (11 vs 10%; P>0.05).
Nicholls et al.[96] (2010) VOYAGER Rosuvastatin (variable doses) vs atorvastatin (variable doses)	MA (37 trials) Patients with hypercholesterolemia	N=32,258 Variable duration	Primary: Impact of increasing dose on lowering LDL-C, TG, non-HDL-C, and apo B Secondary: Not reported	Primary: Increasing doses of all agents resulted in an incremental benefit on LDL-C reduction. The incremental impact of dose doubling was comparable, with a 5% to 7% increase in LDL-C lowering. A greater percentage of patients achieved LDL-C treatment goals using increasing doses of all agents, as well as in patients with lower cholesterol levels at baseline. Increasing doses of all agents resulted in an incremental benefit on TG reduction. The incremental impact of dose doubling was comparable, with a 2

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs simvastatin (variable doses)				to 4% increase in TG lowering. Increasing doses of all agents resulted in an incremental benefit on non-HDL-C reduction. The incremental impact of dose doubling was comparable, with a 4 to 6% increase in non-HDL-C lowering. Increasing doses of all agents resulted in an incremental benefit on apo B reduction. The incremental impact of dose doubling was comparable, with a 4 to 6% increase in apo B lowering. Increasing statin dose was not associated with an increase in withdrawal rates due to adverse events. Secondary: Not reported
Harley et al.[97] (2007) Rosuvastatin, after simvastatin therapy vs atorvastatin, after simvastatin therapy vs lovastatin, after simvastatin monotherapy vs pravastatin, after	RETRO Adult patients ≥18 years of age, receiving simvastatin monotherapy between July 2005 and June 2006, switched to other statin therapy	N=134,160 1 year	Primary: Percentage of patients achieving NCEP ATP III LDL goal after switching from simvastatin to another statin Secondary: Not reported	Primary: Of those patients not at NCEP ATP III LDL goal with simvastatin monotherapy, 73% reached their LDL goal following the switch to another statin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin monotherapy vs fluvastatin, after simvastatin monotherapy vs simvastatin-ezetimibe, after simvastatin monotherapy				
Fox et al.[98] (2007) Rosuvastatin (average dose, 11.7 mg/day) vs other statins (atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin; dosed 17 to 64 mg/day)	RETRO Adult patients with diabetes who were newly prescribed a statin between August 2003 and March 2006	N=4,754 Patients received statin therapy between August 2003 and March 2006	Primary: Percent reduction from baseline in LDL-C, proportion of patients achieving LDL-C goal <100 mg/dL Secondary: Not reported	Primary: Rosuvastatin was associated with a significant reduction in small dense LDL-C compared to atorvastatin (22.5%), simvastatin (20.1%), pravastatin (13.7%), lovastatin (17.3%) and fluvastatin (15.8%) (P<0.0001 for all). Compared to other statins, a significantly greater proportion of patients receiving rosuvastatin achieved the LDL-C goal (P<0.05). Secondary: Not reported
Ballantyne et al.[99] (2007) EXPLORER Ezetimibe 10 mg QD and	MC, OL, PG, RCT Men and women aged ≥18 years with	N=469 6 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal	Primary: Significantly more patients in the combination therapy group achieved the LDL-C goal of <100 mg/dL at week six compared to rosuvastatin alone (94 vs 79.1%; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
rosuvastatin 40 mg QD vs rosuvastatin 40 mg QD	hypercholesterolemia, history of CHD or clinical evidence of atherosclerosis or CHD risk equivalent (10-year CHD risk score >20%), 2 most recent fasting LDL-C levels of ≥160 mg/dL and <250 mg/dL		(<100 mg/dL) after 6 weeks of treatment Secondary: Percentage of patients achieving the ATP III non-HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL, percentage of patients achieving the 2003 European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals of <100 or 115 mg/dL and <175 or 190 mg/dL, respectively, depending on risk category, percentage change from baseline in LDL, HDL, TC, TG, non-	The non-HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL were achieved by a significantly higher percentage of patients in the combination therapy group than the monotherapy group (88 patients or 37.4% and 80 patients or 34.8%, respectively; P<0.001). There was a significantly higher percent of patients in the combination therapy group achieving the European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals (LDL <100 or 115 mg/dL and TC <175 or 190 mg/dL), depending on risk category compared to the rosuvastatin group alone at week six (LDL 93.6 vs 74.3%, LDL and TC 90.6 vs 68.3%, respectively; P<0.001). At week six, the combination therapy group had a significantly greater percent reduction of 69.8% in the LDL level compared to a 57.1% reduction in the monotherapy group (P<0.001). Significantly greater reductions in TC, non-HDL-C and TG levels were seen in the combination group compared to the monotherapy group (P<0.001). Both treatment groups increased HDL level to a similar extent (P=0.151). LDL:HDL, TC:HDL and non-HDL:HDL cholesterol ratios decreased significantly more in patients receiving combination therapy compared to patients receiving monotherapy (all P<0.001). Significant decreases in apo B and the apo B:apo AI ratio were seen in the combination therapy group compared to the monotherapy group (P<0.001 for both). Apo AI increased by 3.2% and 1.6% in the combination therapy and monotherapy groups, respectively (P=0.202). The median percent decrease in CRP was significantly higher with combination therapy than monotherapy (-46.4 vs -28.6%; P<0.001). The overall frequency and type of adverse events were similar in both groups, with 31.5% of patients on combination therapy and 33.5% of patients on monotherapy reporting any adverse event. No adverse events were considered related to ezetimibe; the most frequently reported adverse event was myalgia (3.0% of patients in the rosuvastatin-alone group and 2.9% in the rosuvastatin plus ezetimibe group). There were two patients (0.8%) in the combination therapy group and three patients (1.3%) in the monotherapy group who discontinued the study due to treatment-related adverse events. One death occurred in the combination therapy group due to acute myocardial infarction and this was not considered to be related to study treatment. ALT increases >3 times the upper limit of normal were recorded in three patients, all in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			HDL, lipid ratios (LDL:HDL, TC:HDL and non-HDL:HDL), apo AI, apo B, and apo B:apo AI ratio, and changes in hsCRP in at week six, safety and tolerability	combination therapy group.
Jones et al.[100] (2009) Fenofibric acid 135 mg QD and rosuvastatin (10 or 20 mg) QD vs fenofibric acid 135 mg QD vs rosuvastatin 10, 20, or 40 mg QD	AC, DB, MC, RCT Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=1,445 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP	Primary: Combination therapy (rosuvastatin 10 and 20 mg) was associated with a significantly greater increase in HDL-C (10 mg: 20.3 vs 8.5%; P<0.001 and 20 mg: 19.0 vs 10.3%; P<0.001) and a significantly greater decrease in TG (10 mg: 47.1 vs 24.4%; P<0.001 and 20 mg: 42.9 vs 25.6%; P<0.001) compared to rosuvastatin (10 and 20 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (10 mg: 37.2 vs 6.5%; P<0.001 and 20 mg: 38.8 vs 6.5%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (rosuvastatin 10 mg) was associated with a significantly greater reduction in non-HDL-C compared to fenofibric acid or rosuvastatin (10 mg) (P<0.001). Combination therapy was also associated with significantly greater improvements in VLDL-C (P<0.001), apo B (P<0.001) and hsCRP (P=0.013) compared to rosuvastatin. Combination therapy (rosuvastatin 20 mg) significantly improved non-HDL-C compared to fenofibric acid (P<0.001) and was associated with a significantly greater improvement in VLDL-C (P=0.038) and hsCRP (P=0.010) compared to rosuvastatin (20 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
Roth et al.[101]	DB, MC, RCT	N=760	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2010) Rosuvastatin 5 mg/day vs fenofibric acid 135 mg/day vs rosuvastatin 5 mg/day plus fenofibric acid 135 mg/day	Patients with fasting LDL-C ≥130 mg/dL, TG ≥150 mg/dL and HDL-C 40 mg/dL	12 weeks (plus a 30 day safety follow up period)	Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Changes from baseline in non-HDL-C, VLDL-C, apo B, hsCRP and TC; safety; proportion of patients achieving LDL-C (<100 mg/dL) and non-HDL-C (<130 mg/dL) goals	Combination therapy resulted in a significantly greater mean percent change in HDL-C (23.0 vs 12.4%; *P*<0.001) and TG (-43.0 vs -17.5%; *P*<0.001) compared to rosuvastatin, and resulted in significantly higher mean percent decrease in LDL-C compared to fenofibric acid (28.7 vs 4.1%; *P*<0.001). Secondary: Combination therapy resulted in significantly greater improvements in non-HDL-C compared to either monotherapy, and significantly greater improvements in apo B, hsCRP, VLDL-C and TC compared to rosuvastatin. All treatments were generally well tolerated, with discontinuations due to adverse events being higher with combination therapy (8.3%) and fenofibric acid (7.5%) compared to rosuvastatin (4.4%). The most common adverse events leading to discontinuation were myalgia and muscle spasms and nausea, fatigue and ALT and AST increases. The overall incidence of treatment-emergent adverse events was similar across treatments (58.5 to 63.0%). No significant differences were observed between the combination therapy and either monotherapy in the incidence of any category of adverse events (muscle, hepatic and renal related). In patients with a 10 year CHD risk >20%, the LDL-C goal <100 mg/dL was achieved by 50.5% of patients receiving combination therapy and rosuvastatin; the non-HDL-C goal <130 mg/dL was achieved by 49.5% of patients receiving combination therapy compared to 33.3% of patients receiving rosuvastatin (*P*=0.03). Both LDL-C and non-HDL-C goals were achieved by 44.3 vs 32.3% (*P*=0.10).
Ferdinand et al.[102] (2012) Fenofibric acid 135 mg QD and rosuvastatin 10 mg QD for 12 weeks, followed by fenofibric acid 135 mg QD and rosuvastatin 20	Post-hoc analysis Patients ≥18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women and LDL-C ≥130 mg/dL)	N=187 1 year	Primary: Change in baseline LDL-C, HDL-C, non-HDL-C, apo B, TG, hsCRP; proportion of patients achieving individual and	Primary: Increasing rosuvastatin from 10 to 20 mg, in combination with fenofibric acid for up to 52 weeks, resulted in significant changes from baseline in LDL-C (-9.5%), non-HDL-C (-0.6%), apoB (-8.5%), and HDL-C (3.6%) (P≤0.005 for all). TG levels remained unchanged (0.8%; P=0.055) at week 52. A greater proportion of patients achieved risk-stratified lipid goals at week 52 compared to baseline for LDL-C (89 vs 84%; P=0.26), non-HDL-C (50 vs 25%; P value not reported), and both LDL-C and non-HDL-C (50 vs 19%; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg QD for up to 52 weeks Outcomes were evaluated from the end of the initial 12 week period (baseline) up to 52 weeks of treatment.			combined goals for LDL-C and non-HDL-C; safety Secondary: Not reported	The incidences of muscle-, hepatic-, and renal-related adverse events and laboratory values were within the expected range for combination therapy. The most commonly reported treatment-emergent adverse events (>10%) were upper respiratory tract infection (14.4%), headache (13.9%), and back pain (10.7%)/ Treatment-emergent serious adverse events occurred in seven percent of patients, and one death (MI) occurred, none of which were deemed to be treatment-related. Secondary: Not reported
Mohiuddin et al.[103] (2009) Fenofibric acid 135 mg QD plus simvastatin 20 to 40 mg QD vs fenofibric acid 135 mg QD vs simvastatin 20 to 80 mg QD	AC, DB, MC Patients >18 years of age with mixed dyslipidemia (TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, and LDL-C ≥130 mg/dL)	N=657 16 weeks (includes 30 day safety evaluation)	Primary: Composite of mean percent changes from baseline in HDL-C, TG and LDL-C Secondary: Composite of mean percent changes from baseline in non-HDL-C, VLDL-C, TC, apo B and hsCRP	Primary: Combination therapy was associated with a significantly greater increase in HDL-C (20 mg: 17.8 vs 7.2%; P<0.001 and 40 mg: 18.9 vs 8.5%; P<0.001) and a significantly greater decrease in TG (20 mg: 37.4 vs 14.2%; P<0.001 and 40 mg: 42.7 vs 22.4%; P<0.001) compared to simvastatin (20 and 40 mg). Combination therapy was associated with a significantly greater decrease in LDL-C (20 mg: 24.0 vs 4.0%; P<0.001 and 40 mg: 25.3 vs 4.0%; P<0.001) compared to fenofibric acid. Secondary: Combination therapy (simvastatin 20 mg) was associated with a significantly greater decrease in non-HDL-C (P<0.001) compared to fenofibric acid and simvastatin (20 mg). Combination therapy (simvastatin 20 mg) was associated with significant improvements in VLDL-C (P<0.001), apo B (P<0.001) and hsCRP (P=0.013) compared to simvastatin (20 mg). Combination therapy (simvastatin 40 mg) significantly (P<0.001) improved non-HDL-C compared to fenofibric acid, and resulted in a significantly greater improvement in VLDL-C (P=0.005) compared to simvastatin (40 mg), with similar reductions in non-HDL-C, apo B and TC (P values not reported).
May et al.[104] (2008) DIACOR	DB, PC, RCT Patients with type 2 diabetes, no	N=300 12 weeks	Primary: Lipid and lipoprotein profiles	Primary: Fenofibrate plus simvastatin significantly reduced dense VLDL-C compared to fenofibrate (P<0.001) and simvastatin (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Fenofibrate 160 mg and simvastatin 20 mg QD vs fenofibrate 160 mg QD vs simvastatin 20 mg QD	CHD, and biochemical evidence of mixed dyslipidemia (having 2 of the following 3 lipid parameters: LDL-C >100 mg/dL, TG >200 mg/dL, and HDL-C <40 mg/dL)		Secondary: Not reported	Simvastatin significantly reduced IDL-C compared to fenofibrate (P<0.003). The percentage of LDL-C pattern B constituting total LDL-C was significantly reduced by fenofibrate (-13.7%, P<0.0001) and fenofibrate plus simvastatin (-11.1%, P<0.0001). There was no significant change with simvastatin (-2.4%, P=0.27). Fenofibrate and fenofibrate plus simvastatin significantly increased the percentage of buoyant LDL-C constituting total LDL-C (-19.6%, P<0.0001 and -16.9%, P<0.0001, respectively). There was no significant change with simvastatin (-3.1%, P=0.06). Secondary: Not reported
Derosa et al.[105] (2009) Fenofibrate 145 mg/day and simvastatin 40 mg/day vs fenofibrate 145 mg/day vs simvastatin 40 mg/day	RCT, DB, MC Caucasian patients ≥18 years of age with type 2 diabetes mellitus and combined dyslipidemia who had never been treated with lipid-lowering medications	N=241 12 months	Primary: Lipid and lipoprotein profiles at six and 12 months Secondary: Not reported	Primary: After six months of therapy, there was a significant reduction in TC and LDL-C with simvastatin and fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively). There was no significant change in the fenofibrate group. After 12 months of therapy, there was a significant decrease in TC and LDL-C in all treatment groups (P<0.05 for fenofibrate, P<0.01 for the simvastatin and P<0.001 for fenofibrate plus simvastatin). TC was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). LDL-C was significantly lower with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.01). After six months of therapy, there was a significant reduction in TG with fenofibrate and fenofibrate plus simvastatin (P<0.05, respectively). There was no significant change in the simvastatin group. After 12 months of therapy, there was a significant decrease in TG in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate plus simvastatin). TG was significantly lower with fenofibrate + simvastatin compared to fenofibrate (P<0.05) or simvastatin (P<0.01). After six months of therapy, there was a significant increase in HDL-C with fenofibrate and fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively). There was no change in the simvastatin group. After 12 months of therapy,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				there was a significant increase in HDL-C in all treatment groups (P<0.01 for fenofibrate, P<0.05 for simvastatin and P<0.001 for fenofibrate plus simvastatin). HDL-C was significantly higher with fenofibrate plus simvastatin compared to simvastatin monotherapy and fenofibrate monotherapy (P<0.05). After six months of therapy, there was no significant change in apo A1 or apo B in any treatment group. After 12 months of therapy, there was a significant increase of apo A1 with fenofibrate plus simvastatin. There was no significant difference between the treatment groups. After 12 months of therapy, there was a significant decrease of apo B in all groups (P<0.05 for fenofibrate, P<0.05 for simvastatin and P<0.01 for fenofibrate plus simvastatin). There was no significant difference between the treatment groups. There were no significant differences in Lp(a) after six or 12 months of therapy in any of the treatment groups. After six months of therapy, there was a significant decrease in hsCRP with fenofibrate plus simvastatin (P<0.05), but not in the other groups. After 12 months of therapy, there was a significant decrease in hsCRP with simvastatin and with fenofibrate plus simvastatin (P<0.05 and P<0.01, respectively), but not with fenofibrate. The hsCRP value was significantly lower with fenofibrate plus simvastatin compared to fenofibrate or simvastatin (P<0.05). Secondary: Not reported
Rogers et al.[106] (2007) Simvastatin 10, 20, 40 or 80 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day	MA (18 trials) Patients >18 years of age with elevated TC and LDL-C	N=8,320 Up to 12 weeks	Primary: Reductions in TC, LDL-C and TG; increases in HDL-C Secondary: Not reported	Primary: Simvastatin appeared to be comparable to atorvastatin in terms of TC reduction from baseline at four times the dose of atorvastatin (P>0.05). Simvastatin 20 and 40 mg were less effective at reducing LDL-C from baseline compared to atorvastatin 40 and 80 mg, respectively (P<0.001). Simvastatin 40 to 80 mg was comparable to atorvastatin 20 mg in terms of TG reduction from baseline (P=0.22 and P=0.53, respectively). Atorvastatin 40 to 80 mg was more effective in reducing TG from baseline compared to all simvastatin doses evaluated (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Simvastatin 10, 20 and 80 mg were more effective than atorvastatin 80 mg in increasing HDL-C from baseline (P<0.05). Secondary: Not reported
Hall et al (abstract).[107] (2009) SPACE ROCKET Simvastatin 40 mg/day vs rosuvastatin 10 mg/day	MC, OL, RCT Patients with a history of acute MI	N=1,263 3 months	Primary: Proportion of patients achieving the European Society of Cardiology 2003 TC (<174 mg/dL) or LDL-C (<97 mg/dL) goals Secondary: Not reported	Primary: There was no difference between the two treatments in the proportions of patients who achieved lipid goals (77.6 vs 79.9%; OR, 1.16; 95% CI, 0.88 to 1.53; P=0.29). A post hoc analysis demonstrated a significantly higher achievement of the new European Society of Cardiology, American Heart Association and American College of Cardiology LDL-C goal (<70 mg/dL) with rosuvastatin (37.8 vs 45.0%; OR, 1.37; 95% CI, 1.09 to 1.72; P=0.007). The proportion of patients achieving the Fourth Joint Task Force European Guidelines TC (<155 mg/dL) and LDL-C (<77 mg/dL) goals were also significantly higher with rosuvastatin (38.7 vs 47.7%; OR, 1.48; 95% CI, 1.18 to 1.86; P=0.001). Secondary: Not reported
Feldman et al.[108] (2004) Ezetimibe 10 mg/day plus simvastatin 10, 20 or 40 mg/day vs simvastatin 20 mg/day	DB, MC, RCT Patients 18 to 80 years of age with CHD or CHD risk equivalent disease and LDL-C ≥130 mg/dL and TG ≤350 mg/dL	N=710 23 weeks	Primary: Proportion of patients with LDL-C <100 mg/dL at week five Secondary: Proportion of patients with LDL-C <100 mg/dL at 23 weeks	Primary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week five compared to patients receiving simvastatin (P<0.001). Secondary: A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL at week 23 compared to patients receiving simvastatin (P<0.001). At five weeks, there was a significant reduction in TC, non-HDL-C, apo B, TC:HDL-C and LDL-C:HDL-C with combination therapy compared to simvastatin (P<0.001 for all). HDL-C was significantly increased with combination therapy (10/20 mg) compared to simvastatin (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				At five weeks, combination therapy was associated with a significant reduction in TG compared to simvastatin (P<0.05). Treatment-related adverse effects were similar with simvastatin and combination therapy (10/10, 10/20 and 10/40 mg) (7.5, 9.6, 14.0 and 10.0%, respectively; P values not reported).
Gaudiani et al.[109] (2005) Ezetimibe 10 mg/day plus simvastatin 20 mg/day vs simvastatin 40 mg/day All patients received simvastatin 20 mg/day for a 6 week run in period.	DB, MC, PG, RCT Patients 30 to 75 years of age with type 2 diabetes (HbA_{1c} ≤9.0%), treated with a stable dose of pioglitazone (15 to 45 mg/day) or rosiglitazone (2 to 8 mg/day) for ≥3 months, LDL-C >100 mg/dL and TG <600 mg/dL (if already on a statin therapy)	N=214 30 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and apo AI	Primary: LDL-C was reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin (20.8 vs 0.3%; P<0.001). Secondary: TC (14.5 vs 1.5%; P<0.001), non-HDL-C (20.0 vs 1.7%; P<0.001), apo B (14.1 vs 1.8%; P<0.001), LDL-C:HDL-C (P<0.001), TC:HDL-C (P<0.001) and apo AI (P<0.001) were reduced more by the addition of ezetimibe to simvastatin than by doubling the dose of simvastatin. The increase in HDL-C was similar between the two treatments (P value not reported). The incidence of treatment-related adverse effects was lower with simvastatin compared to combination therapy (10.0 vs 18.3%, respectively; P value not reported).
Bays et al.[110] (2008) Ezetimibe 10 mg/day plus simvastatin 10, 20, 40 or 80 mg/day vs	ES Patients ≥18 years of age with primary hypercholesterolemia	N=768 48 weeks	Primary: Safety and tolerability Secondary: Not reported	Primary: In general, combination therapy did not substantively differ from simvastatin with respect to total adverse events (73 vs 69%), treatment related adverse events (13.5 vs 11.4%), treatment related serious adverse events (1 vs 0%), discontinuations due to treatment related adverse events (2.8 vs 2.6%) or discontinuations due to treatment-related serious adverse events (1 vs 0%). Combination therapy had a slightly higher rate of serious adverse events (5.2 vs 2.6%) and discontinuations due to adverse events (4.5 vs 2.6%) compared to simvastatin (P>0.20). Based on investigator assessment of causality, rates were similar between the treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day				There are no remarkable observations of between-treatment group differences whether or not they are related to a specific tissue or body system. In general, combination therapy did not differ from simvastatin with respect to total laboratory adverse events (12 vs 12%), treatment related laboratory adverse events (6.2 vs 5.3%), total laboratory serious adverse events (0 vs 0%), treatment related laboratory serious adverse events (0 vs 0%) or discontinuations due to laboratory serious adverse events (0 vs 0%). Secondary: Not reported
Calza et al (abstract).[111] (2008) Rosuvastatin 10 mg QD vs pravastatin 20 mg QD vs atorvastatin 10 mg QD	OL, PRO, RCT Patients with HIV receiving protease inhibitor therapy ≥12 months with protease inhibitor-associated hypercholesterolemia ≥3 months and unresponsive to a hypolipidemic diet and physical exercise	N=94 12 months	Primary: Changes from baseline in TC and LDL-C Secondary: Not reported	Primary: Statins led to a mean reduction of 21.2 and 23.6% in TC and LDL-C (P=0.002). The mean decrease in TC was significantly greater with rosuvastatin (25.2%) compared to pravastatin (17.6%; P=0.01) and atorvastatin (19.8%; P=0.03). During the 12 months, all statins demonstrated a favorable tolerability profile, and patient's HIV viral load did not present any variation. Secondary: Not reported
Faergeman et al.[112] (2008) ECLIPSE Rosuvastatin 10 mg for 6 weeks; dose was force-titrated every 6	RCT, OL, MC, PG Patients ≥18 years of age with hypercholesterolemia and a history of CHD, clinical evidence of	N=1,036 24 weeks	Primary: Percentage of patients achieving NCEP ATP III LDL-C goal <100 mg/dL after 24 weeks	Primary: A greater percentage of patients achieved the NCEP ATP III LDL-C goal with rosuvastatin than with atorvastatin at week 24 (83.6 vs 74.6%; P<0.001). Secondary: A greater percentage of patients achieved the NCEP ATP III non-HDL-C goal with rosuvastatin than with atorvastatin (week 6, 41.9 vs 19.6%; week 12, 64.5 vs 32.0%; week 18, 76.0 vs 55.0%; week 24, 79.6 vs 68.0%; P<0.02 at each time point).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
weeks to maximal dose (40 mg) vs atorvastatin 10 mg for 6 weeks; dose was force-titrated every 6 weeks to maximal dose (80 mg) Doses could be decreased for safety reasons.	atherosclerosis or a 10-year CHD risk score >20% (CHD risk equivalent)		Secondary: Percentage of patients achieving NCEP ATP III LDL-C goal <100 mg/dL at weeks 6, 12 and 18; achievement of the following NCEP ATP III goals at all time points: non-HDL-C <130 mg/dL, 2003 European LDL-C goals (100-115 mg/dL and combined LDL-C and TC goals (LDL-C 100-115 mg/dL and TC 175 or 190 mg/dL), percentage changes from baseline in LDL-C, HDL-C, TC, TG, non-HDL-C, and lipid ratios	A greater percentage of patients achieved the 2003 European LDL-C goals and the combined LDL-C and TC goals with rosuvastatin than with atorvastatin at all time points (P<0.001). Significantly greater reductions in LDL-C, TC and non-HDL-C levels, and increases in HDL-C were achieved with rosuvastatin than with atorvastatin at all time points. The reductions in TG levels were similar in both treatment groups at all time points except at week 24, when a significantly greater decrease was observed in patients receiving atorvastatin compared to those receiving rosuvastatin (P<0.05). Significantly greater mean reductions in LDL-C:HDL-C, TC:HDL-C, non-HDL-C:HDL-C and apoB:apo AI ratios were achieved with rosuvastatin than with atorvastatin at all time points (P<0.001). Adverse events were experienced by 53.7 and 52.5% of patients receiving rosuvastatin and atorvastatin, respectively. Myalgia was the most frequently reported adverse events.
Insull et al.[113] (2007) SOLAR	MC, RCT Patients ≥18 years	N=1,632 12 weeks	Primary: Proportion of patients	Primary: After six weeks, a significantly greater proportion of patients receiving rosuvastatin 10 mg achieved the high risk LDL-C goal compared to patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Rosuvastatin 10 mg/day daily for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs atorvastatin 10 mg/day for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved vs simvastatin 20 mg/day for 6 weeks, followed by doubling of the dose and treatment for another 6 weeks if LDL-C target (<100 mg/dL) was not achieved	of age who were enrolled in a managed care health plan and classified as high risk by NCEP ATP III risk assessment		achieving NCEP ATP III high risk LDL-C goal (<100 mg/dL) at week six Secondary: Proportion of patients achieving the high risk LDL-C goal at 12 weeks, proportion of hyper-triglyceridemic patients who achieved both the LDL-C goal (<100 mg/dL) and the non-HDL-C goal (<130 mg/dL) for high risk patients, changes from baseline in LDL-C and other lipid parameters at six and 12 weeks	receiving atorvastatin 10 mg and patients receiving simvastatin 20 mg (65 vs 41 vs 39%, respectively; P<0.001). Secondary: After 12 weeks, 76% of patients receiving rosuvastatin 20 mg achieved the high risk LDL-C goal compared to 58 and 53% of patients receiving atorvastatin 20 mg and simvastatin 40 mg, respectively (P<0.001). After six weeks, 44% of hypertriglyceridemic patients receiving rosuvastatin 10 mg achieved the combined LDL-C and non-HDL-C goals compared to 19% of patients receiving simvastatin 20 mg, respectively (P<0.001). There was no difference between rosuvastatin 10 mg and atorvastatin 10 mg (44 vs 22%; P value not reported). After 12 weeks, 57% of hypertriglyceridemic patients taking rosuvastatin 20 mg reached the combined LDL-C and non-HDL-C goal compared to 31% of patients taking simvastatin 40 mg, respectively (P<0.001). There was no difference between rosuvastatin 20 mg and atorvastatin 20 mg (57 vs 36%; P value not reported). Rosuvastatin was associated with a significant reduction in LDL-C compared to atorvastatin and simvastatin at six and 12 weeks (P<0.001 for both). Rosuvastatin was associated with a significant reduction in TC compared to atorvastatin and simvastatin at six and 12 weeks (P<0.001). Rosuvastatin was associated with a significant reduction in non-HDL-C compared to atorvastatin and simvastatin at six and 12 weeks (P<0.001). Rosuvastatin was associated with a significant reduction in non-HDL-C:HDL-C compared to atorvastatin and simvastatin at six and 12 weeks (P<0.001). Rosuvastatin was associated with a significant increase in HDL-C compared to atorvastatin and simvastatin at 12 weeks (P<0.001). Patients randomized to rosuvastatin experienced a statistically significant reduction in TG from baseline compared to simvastatin at six and 12 months

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
All patients were randomized after a 6 week dietary lead in period.				(P<0.001). The frequency and types of adverse events were similar with all treatments (P value not reported).
Ballantyne et al.[114] (2006) MERCURY II Rosuvastatin 20 mg/day for 8 weeks vs atorvastatin 10 or 20 mg/day for 8 weeks vs simvastatin 20 or 40 mg/day for 8 weeks All patients were randomized after a 6 week dietary lead in period. After 8 weeks of treatment, patients received an additional 8 weeks of either initial statin or	MC, OL, RCT Patients ≥18 years of age, at high risk for CHD events, fasting LDL-C ≥130 to <250 mg/dL on 2 separate measurements within 15% of each other and a fasting TG <400 mg/dL	N=1,993 16 weeks	Primary: The proportion of patients achieving LDL-C <100 mg/dL at week 16 Secondary: The proportion of patients meeting the LDL-C target at week eight, change in lipid and lipoprotein measures at weeks eight and 16, adverse events	Primary: After 16 weeks, a larger proportion of patients receiving rosuvastatin achieved the LDL-C goal compared to patients receiving all other treatments (83, 42, 64, 32 and 56%, respectively; P value not reported). After 16 weeks, significantly more patients who switched to rosuvastatin therapy achieved LDL-C target level <100 mg/dL compared to patients who remained on their initial statin therapy (P<0.001). Secondary: After 16 weeks, patients who switched to rosuvastatin experienced a significant LDL-C reduction from baseline compared to patients remaining on their initial medication regimen (P<0.001). After eight weeks, a significantly greater proportion of patients receiving rosuvastatin achieved the LDL-C goal <100 mg/dL compared to patients receiving all other treatments (82, 43, 62, 33 and 55%, respectively; P<0.0001). After 16 weeks, a significantly greater proportion of patients randomized to rosuvastatin achieved the LDL-C goal <70 mg/dL compared to patients receiving all other treatments (37, 7, 13, 1 and 10%, respectively; P value not reported). After 16 weeks, patients who switched to rosuvastatin experienced a significant atherogenic lipid measure and ratio reduction from baseline compared to patients remaining on their initial medication regimen (P<0.001). After 16 weeks, a significantly greater proportion of hypertriglyceridemic patients receiving rosuvastatin achieved the LDL-C goal <100 mg/dL and non-HDL-C goals compared to patients receiving all other treatments (80, 20, 42, 19 and 29%, respectively; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
rosuvastatin therapy.				The frequency and type of adverse events were similar with all treatments (P value not reported). In addition, there were no symptomatic adverse events associated with hepatic dysfunction.
Jones et al.[115] (2003) STELLAR Rosuvastatin 10 to 40 mg/day vs pravastatin 10 to 40 mg/day vs atorvastatin 10 to 80 mg/day vs simvastatin 10 to 80 mg/day	OL, PG Patients ≥18 years of age with hypercholesterolemia and LDL-C ≥160 to <250 mg/dL at the 2 most recent consecutive visits	N=2,431 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent changes from baseline in HDL-C, TG and TC	Primary: Compared to all doses of atorvastatin and pravastatin, rosuvastatin was associated with a greater reduction in LDL-C (P<0.001 for both). When compared to baseline, the following reductions in LDL-C were observed: rosuvastatin; 45.8 to 55.0%, atorvastatin; 36.8 to 51.1%, simvastatin; 28.3 to 45.8% and pravastatin; 20.1 to 29.7%. The greatest reductions in LDL-C observed were a 55% reduction with rosuvastatin 40 mg and a 51% reduction with atorvastatin 80 mg (P=0.006). Secondary: Rosuvastatin 10 to 40 mg/day was associated with a 7.7 to 9.6% increase in HDL-C, a 19.8 to 26.1% reduction in TG and a 32.9 to 40.2% reduction in TC (P values not reported). Pravastatin 10 to 40 mg/day was associated with a 3.2 to 5.6% increase in HDL-C, a 7.7 to 13.2% reduction in TG and a 14.7 to 21.5% reduction in TC (P value not reported). Atorvastatin 10 to 80 mg/day was associated with a 2.1 to 5.7% increase in HDL-C, a 20.0 to 28.2% reduction in TG and a 27.1 to 38.9% reduction in TC (P value not reported). Simvastatin 10 to 80 mg/day was associated with a 5.2 to 6.8% increase in HDL-C, an 11.9 to 18.2% reduction in TG and a 20.3 to 32.9% reduction in TC (P value not reported).
McKenney et al.[116] (2007) COMPELL Rosuvastatin 10 mg/day for 4	MC, OL, PG, RCT Patients ≥21 years of age with hyper-cholesterolemia, eligible for	N=292 12 weeks	Primary: Change from baseline in LDL-C Secondary: Change from	Primary: Atorvastatin plus niacin SR, rosuvastatin plus niacin SR, simvastatin plus ezetimibe and rosuvastatin were associated with similar reductions in LDL-C (56, 51, 57 and 53%, respectively; P=0.093). Secondary: Atorvastatin plus niacin SR was associated with a significant increase in HDL-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
weeks, followed by 20 mg/day for 4 weeks, followed by 40 mg/day vs atorvastatin 20 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by atorvastatin 20 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day vs simvastatin 20 mg/day plus ezetimibe 10 mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10 mg/day vs rosuvastatin 10	treatment based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL		baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects	C compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (22, 10 and 7%, respectively; P≤0.05). There was no significant differences in the reduction of non-HDL-C from baseline with any treatment (P=0.053). Atorvastatin plus niacin SR was associated with a significant reduction in TG compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (47, 33 and 25%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in Lp(a) compared to simvastatin plus ezetimibe and rosuvastatin (20 mg)-containing therapy (-14, 7 and 18%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in apo B compared to rosuvastatin (43 vs 39%, respectively; P≤0.05). Side effects were similar across treatments (P values not reported). There were no cases of myopathy or hepatotoxicity reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day plus niacin SR 500 mg/day for 4 weeks, followed by rosuvastatin 10 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by rosuvastatin 20 mg/day plus niacin SR 1,000 mg/day				
Bays et al.[117] (2008) Fenofibric acid 135 mg plus moderate dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) Extension study patients received the same type of statin that was used in the statin-containing arms of the controlled study in which they participated.	MC, OL Patients with mixed dyslipidemia completing 1 of 3 MC, PRO, DB, RCT 12-week studies were eligible	N=2,201 1 year	Primary: Safety, percent changes from baseline in TG, HDL-C, and LDL-C Secondary: Percent changes in non-HDL-C, VLDL-C, TC, apoB, and hsCRP	Primary: Of the 2,201 patients who received at least one dose of fenofibric acid plus statin combination therapy, six patients (0.3%) died during the conduct of the ES; no death was considered by the investigator to be treatment related. Overall, 148 (6.7%) patients had treatment-emergent serious adverse events (fenofibric acid plus rosuvastatin, 7.2%; fenofibric acid plus simvastatin, 7.8%; fenofibric acid plus atorvastatin 4.6%). The most common treatment-emergent serious adverse events were osteoarthritis, deep vein thrombosis, coronary artery disease, MI, and chest pain, diverticulitis, syncope, and intervertebral disc protrusion. A total of 1,856 patients (84.3%) had one or more treatment-emergent adverse events (fenofibric acid plus rosuvastatin, 83.1%; fenofibric acid plus simvastatin, 86.2%; fenofibric acid plus atorvastatin, 85.2%). The most frequently reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, and back pain. Among patients who received fenofibric acid monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-22.0%), mean percent decrease in LDL-C (-38.1%), and mean percent increase in HDL-C (6.2%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Among patients who received moderate-dose statin monotherapy in a controlled study, treatment with fenofibric acid plus moderate-dose statin combination therapy for 52 weeks resulted in an additional median percent decrease in TG (-30.5%) and mean percent increases in HDL-C (13.1%) and LDL-C (3.1%). Among patients who received fenofibric acid plus low-dose statin combination therapy in a controlled study, there was an additional median percent decrease in TG (-4.2%), mean percent increase in HDL-C (4.8%), and mean percent decrease in LDL-C (-9.7%) after the statin dose was increased for 52 weeks. The group of patients who were treated with fenofibric acid plus moderate-dose statin in a controlled study and continued the same therapy in the extension study exhibited sustained improvements in lipid parameters throughout the course of therapy. For this group of patients, treatment with fenofibric acid plus moderate-dose statin combination therapy for a total of 64 weeks decreased TG from a mean baseline of 297.8 mg/dL to a mean final level of 138.0 mg/dL, decreased LDL-C from a mean baseline of 153.1 mg/dL to a mean final level of 94.2 mg/dL, and increased HDL-C from a mean baseline of 38.2 mg/dL to a mean final level of 47.7 mg/dL. Secondary: Among patients who received fenofibric acid monotherapy or moderate-dose statin monotherapy in the controlled studies, treatment with fenofibric acid plus moderate-dose statin combination therapy in the extension study resulted in additional mean percent decreases in non-HDL-C, VLDL-C, TC, and apo B, and median percent decrease in hsCRP that were sustained throughout 52 weeks of combination therapy. For patients initially treated with fenofibric acid plus low-dose statin combination therapy, increasing the statin dose resulted in additional mean percent decreases in non-HDL-C, TC, and apo B and median percent decrease in hsCRP, which were sustained throughout the study.
Kipnes et al.[118] (2010) Fenofibric acid	ES, OL Patients with mixed	N=310 1 year (2 years of total	Primary: Safety and efficacy	Primary: No deaths occurred during the two year trial. The incidence of serious adverse events was numerically highest with fenofibric acid plus rosuvastatin (14.9%) compared to fenofibric acid plus simvastatin (8.0%) or atorvastatin (5.8%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
135 mg/day plus a moderate dose statin (rosuvastatin 20 mg/day, simvastatin 40 mg/day or atorvastatin 40 mg/day)	dyslipidemia at the start of a 1 year, ES, OL	therapy)	Secondary: Not reported	The incidences of adverse events were similar among all treatments as well (94.8, 90.0 and 97.7%). Adverse events tended to occur early in treatment, without the development of new types of adverse events over time. The most common treatment-related adverse events were muscle spasms (3.9%), increased blood creatine phosphokinase (3.5%), headache (2.9%), myalgia (2.9%), dyspepsia (2.3%) and nausea (2.3%). Rhabdomyolysis was not reported with any treatment. Nine patients discontinued therapy due to adverse events, with similar incidences among all treatments. Myalgia was the most common reason for discontinuation. No significant difference in the incidence of laboratory elevations was observed among the treatment groups. Incremental improvements in mean percentage changes in all efficacy variables were observed after the first visit in the year one ES (week 16). This effect was sustained for greater than two years and sizable mean percentage changes in all efficacy variables were observed at week 116. In the overall population, the mean percentage changes from baseline to week 116 in efficacy variables were: 17.4 (HDL-C), -46.4 (TG), -40.4 (LDL-C), -47.3 (non-HDL-C), -37.8 (TC) and -52.8% (VLDL-C). Significant differences among treatments were observed for non-HDL-C (-48.60±13.58 vs -41.70±13.10 vs -47.30±12.50%; P=0.011), TC (-38.70±12.16 vs -32.50±10.86 vs -38.60±10.85%; P=0.007) and VLDL-C (-56.80±25.17 vs -40.30±51.25 vs -51.20±35.42%; P=0.019). Secondary: Not reported
Alrasadi et al.[119] (2008) <u>Protocol 1</u> Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected	N=19 32 weeks	Primary: Percent changes in HDL-C and TC/HDL-C ratio Secondary: Not reported	Primary: <u>Protocol 1</u> The mean percent change in HDL-C was +6, -6, and +22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +19, -26, and -22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). <u>Protocol 2</u>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
weeks vs niacin SR 1 g BID for 8 weeks Protocol 2 Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID and atorvastatin 20 mg/day for 8 weeks Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study in Protocol 2.	with HDL deficiency			The mean percent change in HDL-C was -2 and +18% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +32 and -32% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC/HDL-C (P<0.01). Secondary: Not reported
Jones et al.[120] (2009) Fenofibric acid 135 mg QD vs	Pooled analysis of 3 AC, DB, MC, RCT Patients >18 years of age, with HDL-C <40 mg/dL	N=2,715 12 weeks	Primary: Mean percent change in HDL-C, TGs (fenofibric acid plus atorvastatin vs	Primary: Fenofibric acid plus low-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (18.1 vs 7.4%; P<0.001) and a greater mean percent decrease in TG (-43.9 vs -16.8%; P<0.001) compared to low-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-33.1 vs -5.1%; P<0.001) compared to fenofibric acid monotherapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs fenofibric acid 135 mg plus low-dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg) QD vs moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg) QD vs fenofibric acid 135 mg QD plus moderate-dose statin QD	(men) or <50 mg/dL (women), TGs ≥150 mg/dL, and LDL-C ≥130 mg/dL ≥130 mg/dL		atorvastatin), and LDL-C (fenofibric acid plus atorvastatin vs fenofibric acid) Secondary: Mean percent change in non-HDL-C, VLDL-C, TC, apo B, and hsCRP; safety	Fenofibric acid plus moderate-dose statin combination therapy resulted in a greater mean percent increase in HDL-C (17.5 vs 8.7%; P<0.001) and a greater mean percent decrease in TG (-42.0 vs -23.7%; P<0.001) compared to moderate-dose statin monotherapy, and a greater mean percent decrease in LDL-C (-34.6 vs -5.1%; P<0.001) compared to fenofibric acid monotherapy. No formal comparisons were made between the high-dose statin monotherapy group and the other treatment groups. Secondary: Greater improvements in non-HDL-C, VLDL-C, TC, and apo B were observed for fenofibric acid plus low-dose statin combination therapy compared to corresponding monotherapies (P≤0.001). Combination therapy was generally well tolerated, and safety profiles were similar to monotherapies. No rhabdomyolysis was reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs high-dose statin (rosuvastatin 40 mg, simvastatin 80 mg, or atorvastatin 80 mg) QD				
Bays et al.[121] (2010) COMBOS Omega-3-acid ethyl esters (Lovaza®) 4 g/day plus simvastatin 40 mg/day Patients who received placebo in the COMBOS trial were switched to OL treatment with omega-3-acid ethyl esters plus simvastatin (Switchers). Those who received omega-3-acid ethyl esters plus simvastatin in the COMBOS trial were maintained on current therapy	ES, OL of COMBOS Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥8 weeks prior to trial enrollment	N=188 Up to 24 months	Primary: The difference between Nonswitchers and Switchers in median percent change in non-HDL-C from COMBOS end of treatment to month four Secondary: Difference in the median percent change in non-HDL-C from COMBOS end of treatment to month 12 and 24; the change in non-HDL-C from COMBOS baseline to months four, 12 and 24 and from COMBOS	Primary: The percent change in non-HDL-C from COMBOS end of treatment to month four revealed a greater response among Switchers when compared to Nonswitchers. At month four, the median percent change in non-HDL-C from the end of DB treatment was -9.4% in Switchers and 0.9% in Nonswitchers (P<0.001). Secondary: After 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS end of treatment in Nonswitchers vs Switchers was -0.2 vs -0.64% (P=0.027) and 1.6 vs -6.3% (P=0.004). Reductions in non-HDL-C were maintained throughout the trial. After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in the total population was -8.3, -7.3 and -8.9%, respectively (P<0.001 for all). After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in Nonswitchers vs Switchers was -5.4 vs -10.3% (P=0.062), -6.6 vs -8.1% (P=0.604) and -7.8 vs -9.0% (P=0.496). Consistent with the non-HDL-C response, comparisons of the changes from the COMBOS end of treatment to months four, 12 and 24 in TG and other lipoprotein lipid parameters generally revealed greater reductions in Switchers vs Nonswitchers. The comparisons of the change from COMBOS baseline to these same endpoints reveled generally nonsignificant differences between the two groups. Median percent reductions from COMBOS baseline in TG, TC and VLDL-C in the total population were maintained at months four, 12 and 24 of treatment (P<0.001 for all). Omega-3-acid ethyl esters produced small median percent increases from baseline LDL-C levels at months four, 12 and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(Nonswitchers) All patients continued therapeutic lifestyle changes diet.			end of treatment to months four, 12 and 24; percent changes in TC, HDL-C, LDL-C, VLDL-C, TG and TC:HDL-C for the same time points; HbA_{1c} levels	24. Among the subset of patients who had HbA_{1c} measured at baseline (n=38), the median absolute change in HbA_{1c} after 24 months of treatment was 0.1% (P value not reported).
Hypertriglyceridemia (Single Entity Agents)				
Hogue et al.[122] (2008) Fenofibrate 200 mg QD vs atorvastatin 20 mg QD	RCT Patients with type 2 diabetes and hypertriglyceridemia	N=40 6 weeks	Primary: Lipids and TRL, inflammation and adhesion molecules Secondary: Not reported	Primary: Treatment with atorvastatin led to a significant decrease in plasma TC (-37.7%; P<0.0001), plasma TG (-37.6%; P<0.0001), plasma apo B (-43.2%; P<.0001), TRL-C (-44.1%; P<0.0001), TRL-TG (-36.9%; P<0.0001), TRL apo B (-13.8%; P=0.04), LDL-C (-43.0%; P<0.0001), LDL apo B (-42.7%; P<0.0001), and a significant increase in HDL-C (17.9%; P=0.001), and HDL apo A-I levels (10.3%; P=0.004). Treatment with fenofibrate led to a significant decrease in plasma C (-10.9%; P=0.0001), plasma TG (-41.4%; P=0.0002), plasma apo B (-9.9%; P=0.01), TRL-C (-52.8%; P<0.0001), TRL-TG (-46.3%; P=0.0002), and TRL apo B (-14.8%; P=0.02) and a significant increase in LDL-C (15.9%; P=0.04) and HDL-C (8.9%; P=0.05). There were significant differences in the percentage changes of plasma cholesterol, plasma apo B, LDL-C, and LDL apo B between the two treatment groups. There was no significant difference in the percentage in changes of plasma TG between the treatment groups. Treatment with atorvastatin significantly decreased plasma levels of CRP (-26.9%; P=0.004), soluble ICAM-1 (-5.4%; P=0.03), soluble VCAM-1 (-4.4%; P=0.008), soluble E-selectin (-5.7%; P=0.02), MMP-9 (-39.6%; P=0.04), soluble phospholipase A2 (-14.8%; P=0.04), and oxidized LDL (-38.4%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Fenofibrate significantly decreased soluble E-selectin levels only (-6.0, P=0.04) and increased soluble phospholipase A2 levels (22.5%; P=0.004). Secondary: Not reported
Hypercholesterolemia Clinical Outcomes Trials (Single Entity Agents)				
Delaying the Progression of Atherosclerosis (Single Entity Agents)				
Nissen et al.[123] (2006) ASTEROID Rosuvastatin 40 mg QD	MC, OL, PRO Patients ≥18 years of age requiring coronary angiography for a stable or unstable ischemic chest pain syndrome or abnormal exercise test, with ≥1 obstruction ≥20% angiographic luminal diameter narrowing in a coronary vessel, not on statin therapy for >3 months within the last 12 months	N=507 24 months	Primary: PAV, absolute change in TAV in the 10 mm subsegment of the coronary artery with the largest plaque volume at baseline Secondary: Change in normalized TAV, lipid parameters	Primary: Rosuvastatin achieved a significant reduction in PAV from baseline (-0.79%; 95% CI, -1.21 to -0.53; P<0.001). Rosuvastatin achieved significant reduction from baseline in atheroma volume in the most diseased 10 mm subsegment (-5.6 mm^3; 95% CI, -6.82 to -3.96; P<0.001). Secondary: Rosuvastatin achieved a significant reduction from baseline in normalized TAV (-12.5 mm^3; 95% CI, -15.08 to -10.48; P<0.001). Rosuvastatin achieved a significant reduction from baseline in the total normalized TAV (-6.8%; 95% CI, -7.82 to -5.60; P<0.001). Rosuvastatin achieved a significant reduction from baseline in TC (33.0%), LDL-C (53.2%), TG (14.5%), LDL-C:HDL-C ratio (58.5%) and non-HDL-C (47.2%; P<0.001). Rosuvastatin achieved a significant increase from baseline in HDL-C (14.7%; P<0.001).
Furberg et al.[124] (1994) ACAPS Lovastatin 20 to 40 mg QD plus warfarin 1 mg QD	DB, MC, PC, RCT Asymptomatic patients 40 to 79 years of age, with early carotid atherosclerosis as	N=919 3 years	Primary Three year change in the mean maximum IMT in 12 walls of the carotid arteries (near and far walls of	Primary The progression rate of mean maximum IMT was less with lovastatin plus warfarin than with lovastatin (P=0.04). The overall annualized progression rates of mean maximum IMT with lovastatin and placebo were -0.009 and 0.006 mm/year, respectively (P=0.001). Secondary: The changes in single maximum IMT with lovastatin and placebo were -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs lovastatin 20 to 40 mg QD plus warfarin placebo vs lovastatin placebo plus warfarin 1 mg QD vs lovastatin placebo plus warfarin placebo	defined by B-mode ultrasonography and moderately elevated LDL-C (between the 60th and 90th percentiles)		the common carotid, the bifurcation and the internal carotid arteries on both sides of the neck) Secondary Change in single maximum IMT, incidence of major cardiovascular events and adverse events	0.036±0.022 and 0.000±0.011 mm/year, respectively (P=0.12). Fourteen of the 459 patients receiving lovastatin-placebo had a major cardiovascular event (four CHD deaths, five strokes and five nonfatal MI) compared to five of the 460 patients receiving placebo (P=0.04). There was one death in patients receiving lovastatin and eight in patients receiving lovastatin plus placebo (P=0.02). All six cardiovascular deaths were with lovastatin plus placebo, the remaining three deaths were cancer deaths. Lovastatin and lovastatin-placebo demonstrated no difference in ALT elevations of ≥200% the upper limit of normal.
Byington et al.[125] (1995) PLAC-II Pravastatin 20 mg QD in the evening, titrated up to 40 mg/day vs placebo	DB, PC, RCT Patients with a history of CHD and ≥1 extracranial carotid lesion with the maximum IMT ≥1.3 mm	N=151 3 years	Primary: Change in the mean of maximum IMT measurements in the common, internal and bifurcation carotid artery segments Secondary: Effects on individual carotid artery segments and clinical events	Primary: Pravastatin did not result in a significant reduction in the progression of mean maximum IMT (P=0.44). Pravastatin was associated with a significant 35% reduction in IMT progression in the common carotid artery (P=0.03). There was no significant effect on bifurcation (P=0.49) or on the internal carotid artery (P=0.93) with pravastatin. Secondary: Pravastatin was associated with a 60% reduction in clinical coronary events (P=0.09). When compared to placebo, a significant 61% reduction in the incidence of any coronary events and all-cause mortality was seen with pravastatin (P=0.04).
Yu et al.[126] (2007)	DB, RCT Patients with	N=112 26 weeks	Primary: Improvement in IMT	Primary: Atorvastatin 10 mg was not associated with a significant improvement in either left or right carotid IMT (P value not reported). Atorvastatin 80 mg led

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 80 mg QD vs atorvastatin 10 mg QD	CHD (confirmed by angiographic evidence of coronary stenosis, previous MI, PCI or angina pectoris), hypercholesterolemia and LDL-C >100 mg/dL		Secondary: Reduction in hsCRP level, proinflammatory cytokines at week 26	to a significant improvement in left carotid IMT (P=0.02) as well as the right carotid IMT from baseline (P=0.01). Secondary: Atorvastatin 10 mg was not associated with a significant change in hsCRP (P value not reported). Atorvastatin 80 mg led to a significant reduction in hsCRP level from baseline (P=0.01). Atorvastatin 10 mg was associated with a significant reduction in interleukin-8 (P=0.01), interleukin-18 (P<0.001) and tumor necrosis factor (P<0.001). Atorvastatin 80 mg led to a significant reduction in all the proinflammatory cytokines from baseline (P<0.05).
Schmermund et al.[127] (2006) Atorvastatin 10 mg QD vs atorvastatin 80 mg QD	DB, MC, RCT Patients 32 to 80 years of age without a history of MI, coronary revascularization or hemodynamically relevant stenoses, with moderate calcified coronary atherosclerosis (coronary artery calcification score ≥30), LDL-C 130 to 250 mg/dL in the absence of statin therapy or between 100 to 130 mg/dL under statin therapy, TG <400 mg/dL, ≥2 cardiovascular risk factors	N=471 12 months	Primary: The percent change in total coronary artery calcification volume score Secondary: Change in LDL-C	Primary: There was no significant difference in the primary endpoint between the two treatments (P=0.6477). Secondary: Atorvastatin 80 mg was associated with a 20% reduction in LDL-C compared to atorvastatin 10 mg (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Crouse et al.[128] (2007) METEOR Rosuvastatin 40 mg QD vs placebo	DB, RCT Patients 45 to 70 years of age with LDL-C 120 to 190 mg/dL among patients whose only CHD risk factor was age, and an LDL-C 120 to 160 mg/dL for patients with ≥2 CHD risk factors and a 10 year risk of CHD events of <10%, HDL-C ≤60 mg/dL, TG <500 mg/dL and maximum CIMT 1.2 to 3.5 mm from 2 separate ultrasounds	N=984 2 years	Primary: Annualized rate of change in maximum CIMT of the 12 carotid artery sites (near and far walls of the right and left common carotid artery, carotid bulb and internal carotid artery) Secondary: Annualized rate of change in maximum CIMT of the common carotid artery, carotid bulb and internal carotid artery sites; annualized rate of change in mean CIMT	Primary: Rosuvastatin was associated with a significant reduction in the annualized rate of change in maximum CIMT from baseline compared to placebo (P<0.001). Secondary: Rosuvastatin was associated with a significant 49% reduction in LDL-C from baseline compared to placebo (P<0.001). Rosuvastatin was associated with a significant reduction in the annualized rate of change in the maximum CIMT for the common carotid artery sites (P<0.001), carotid bulb (P<0.001) and internal carotid artery sites (P=0.02) from baseline compared to placebo. Rosuvastatin was associated with a significant reduction in the annualized rate of change in the mean CIMT for the common carotid artery sites (P<0.001) from baseline compared to placebo.
Chan et al.[129] (2010) ASTRONOMER Rosuvastatin 40 mg/day vs	DB, PC, RCT Patients 18 to 82 years of age with asymptomatic mild to moderate aortic stenosis	N=269 3 to 5 years	Primary: Hemodynamic parameters of aortic stenosis severity Secondary: Composite of aortic valve	Primary: Progression of aortic stenosis measured by the peak gradient and aortic valve area did not differ between the two treatments (P values not reported). The mean changes in the peak aortic stenosis gradient, mean gradient and aortic valve area were no significantly different between the two treatments (P=0.32, P=0.49 and P=0.79, respectively). The annual increase in peak aortic stenosis was 6.1±8.2 and 6.3±6.9 mm Hg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo			replacement and cardiac death	with placebo and rosuvastatin (P=0.83). The annual increase in the mean gradient was 3.9±4.9 and 3.8±4.4 mm Hg with placebo and rosuvastatin (P=0.79). The annual decrease in aortic valve area was 0.08±0.21 and 0.07±0.15 cm^2 (P=0.87). The linear mixed models did not show any significant differences in the primary outcomes between the two treatments at any time point during the follow up. Secondary: There were a total of seven cardiac deaths, one of which was associated with aortic valve replacement, and a total of 55 patients with aortic valve replacement. The survival curves of the outcome events (cardiac death or aortic valve replacement) were not significantly different between the two treatments (P=0.45).
Nissen et al.[130] (2004) REVERSAL Atorvastatin 40 mg BID vs pravastatin 40 mg QD	DB, MC, RCT Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target	N=654 18 months	Primary: Percentage change in atheroma volume from baseline Secondary: Nominal change in atheroma volume, nominal change in atheroma volume in the 10 contiguous cross-sections	Primary: Atorvastatin was associated with a significant delay in atheroma volume progression compared to pravastatin (P=0.02). Secondary: Atorvastatin was associated with a significant nominal change in total atheroma volume compared to pravastatin (P=0.02). Atorvastatin was associated with a significant change in the percentage of atheroma volume compared to pravastatin (P<0.001). Atorvastatin was associated with a significant change in atheroma volume in the most severely diseased 10 mm vessel subsegment compared to pravastatin (P=0.01). Progression of coronary atherosclerosis from baseline occurred in 2.7% of pravastatin-treated patients (P=0.001) and none of the atorvastatin-treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	segment >30 mm long		with the greatest and the least atheroma volume	patients (P=0.98). Atorvastatin 80 mg was associated with a significant reduction in TC, LDL-C, TG, apo B and hsCRP (P<0.001) compared to the pravastatin.
Schoenhagen et al.[131] (2006) REVERSAL Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Serial intravascular ultrasound observations from the REVERSAL trial Patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long	N=654 18 months	Primary: Percentage change from baseline in external elastic membrane area lesion, lumen area lesion, plaque area lesion and remodeling ratio Secondary: Not reported	Primary: Atorvastatin was associated with a significant 6.6% increase in the external elastic membrane area lesion from baseline (P<0.0001). Atorvastatin was associated with a significant 7.3% increase in the lumen area lesion from baseline (P=0.0002). Atorvastatin was associated with a significant 7.9% increase in the plaque area lesion from baseline (P=0.0002). Atorvastatin was associated with a significant 3.3% reduction in remodeling ratio from baseline (P=0.024). Pravastatin was associated with a significant 9% increase in the external elastic membrane area lesion from baseline (P=0.0002). Pravastatin was associated with a significant 9.5% increase in the lumen area lesion from baseline (P=0.0003). Pravastatin was associated with a significant 9.9% increase in the plaque area lesion from baseline (P=0.0022). Pravastatin was associated with a significant 2.7% reduction in remodeling ratio from baseline (P=0.0013). There was no significant difference between atorvastatin and pravastatin in terms of increase in plaque area from baseline (7.9 vs 9.9%, respectively; P=0.57). There was no significant difference between atorvastatin and pravastatin in terms of reduction in remodeling ratio from baseline (3.3 vs 2.7%, respectively; P=0.68).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported
Nicholls et al[132] (2006) REVERSAL Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Subanalysis of REVERSAL trial Obese patients 30 to 75 years of age with >1 angiographic luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI >29.6 kg/m^2 or BMI <29.6 kg/m^2	N=654 18 months	Primary: Percentage change from baseline in lipid parameters, atheroma volume Secondary: Not reported	Primary: Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly lower reduction in TC (40 vs 36%; P=0.007), LDL-C (55 vs 49%; P=0.008) and TG (35 vs 23%; P=0.04). Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly higher reduction in hsCRP (33 vs 40%; P=0.04). There was no significant difference in lipid parameters between the BMI groups among patients randomized to pravastatin (P>0.05). Compared to the BMI <29.6 kg/m^2 group, obese patients receiving atorvastatin exhibited a significantly greater benefit on the total atheroma volume (P=0.01) and percent atheroma volume (P=0.0005). In contrast, pravastatin was associated with a significant 6.5% increase in atheroma volume in the obese group (P=0.006). Secondary: Not reported
Nissen et al.[133] (2005) REVERSAL Atorvastatin 40 mg BID vs pravastatin 40 mg QD	Subanalysis of REVERSAL trial evaluating the effect of statin therapy on LDL-C, hsCRP and CAD Patients 30 to 75 years of age with >1 angiographic	N=654 18 months	Primary: Percent change in TC, TG, CRP, non-HDL-C, HDL-C and atheroma volume Secondary: Not reported	Primary: Both treatments achieved a significant reduction from baseline in TC (63%; P<0.001), LDL-C (56%; P<0.001), TG (40%; P=0.002), CRP (22.4%; P<0.001) and non-HDL-C (33%; P<0.001). HDL-C was not significantly increased from baseline with either treatment (4.2%; P=0.11). Atorvastatin exhibited a slower rate of disease progression (atheroma volume) compared to pravastatin (0.2 vs 1.6%; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	luminal narrowing ≥20% in diameter in a major epicardial coronary artery and an LDL-C 125 to 210 mg/dL; the vessel for analysis was required to have no stenosis >50% in a target segment >30 mm long, stratified based on BMI >29.6 kg/m^2 or BMI <29.6 kg/m^2			Patients whose LDL-C and hsCRP reductions were greater than the median experienced a significantly slower rate of disease progression compared to patients with lower LDL-C and hsCRP reductions (P=0.001). Secondary: Not reported
Meaney et al.[134] (2009) VYCTOR Pravastatin 40 mg QD (ezetimibe 10 mg/day could be added if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions) vs simvastatin 40 mg QD (dose could be increased to 80 mg/day if LDL	RCT, OL Patients 40 to 72 years of age with a 10-year absolute risk for coronary death or myocardial infarction ≥20 according to the ATP III recommendations	N=90 1 year	Primary: Change in CIMT Secondary: Changes in LDL-C and hsCRP	Primary: After one year, CIMT values were 0.93mm (-30%; P<0.01 vs baseline), 0.90 mm (-30%; P<0.01 vs baseline), and 0.92 mm (-25%; P<0.01 vs baseline) for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively. There was no significant difference among the treatment groups. Secondary: At the end of the study, LDL-C levels were 48, 45, and 48 mg/dL for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively (P<0.01 vs baseline for all). There was no significant difference among the treatment groups. The proportion of diabetic patients who attained LDL-C <70 mg/dL at the end of the trial were 62, 80, and 78% for pravastatin, simvastatin, and simvastatin-ezetimibe groups, respectively (P values not significant). There was no significant difference among the treatment groups. There were no significant differences in hsCRP, HDL-C, TG among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
<100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions) vs simvastatin-ezetimibe 20-10 mg QD (dose of simvastatin could be increased to 40 mg/day if LDL <100 mg/dL if they had CHD or diabetes or <70 mg/dL if they had both conditions)				
Primary Prevention of Coronary Heart Disease (Single Entity Agents)				
Knopp et al.[135] (2006) ASPEN Atorvastatin 10 mg QD vs placebo	DB, MC, PG, RCT Patients 40 to 75 years of age with type 2 diabetes for ≥3 years prior to screening, LDL-C ≤140 (if they had a history of an MI or an interventional procedure >3 months before screening) or ≤160 mg/dL, TG ≤600 mg/dL	N=2,410 4 years	Primary: Time to occurrence of the composite clinical endpoint including cardiovascular death, nonfatal MI, nonfatal stroke, recanalization, CABG surgery, resuscitated cardiac arrest or worsening or unstable angina	Primary: There was no significant difference between the two treatments in the time to first primary event (HR, 90; 95% CI, 0.73 to 1.12; P=0.034). Less patients receiving atorvastatin experienced the primary endpoints compared to patients receiving placebo (13.7 vs 15.0%; P=0.034). Secondary: Atorvastatin was associated with a significant decrease in LDL-C compared to placebo (29.0 vs 1.6%; P<0.0001). Among patients without a prior history of an MI or interventional procedure, 10.4 and 10.8% of atorvastatin- and placebo-treated patients experienced a primary endpoint (HR, 97; 95% CI, 0.74 to 1.18). Among patients with a prior history of an MI or interventional procedure, 26.2 and 30.8% of atorvastatin- and placebo-treated patients experienced a primary

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			requiring hospitalization Secondary: Time to occurrence of cardiovascular death, noncardiovascular death, TIA, worsening or unstable angina not requiring hospitalization, worsening or unstable angina requiring hospitalization, surgery for newly diagnosed PAD and acute ischemic heart failure requiring hospitalization; cholesterol level reduction; safety	endpoint (HR, 82; 95% CI, 0.59 to 1.15). RR reductions in fatal and nonfatal MI were 27% overall (P=0.10), 19% for patients treated for primary protection (P=0.41) and 36% for patients treated for secondary protection (P=0.11). Adverse events were similar in both treatments for the total, primary and secondary prevention groups (P value not reported). Serious adverse events occurred in 37.7 and 35.4% of atorvastatin- and placebo-treated patients (P value not reported).
Colhoun et al.[136] (2004) CARDS Atorvastatin 10 mg/day vs	DB, MC, RCT Patients 40 to 75 years of age with type 2 diabetes without a history of CHD, LDL-C ≤160 mg/dL, TG	N=2,838 3.9 years	Primary: Incidence of major cardiovascular events (CHD death, nonfatal MI, including silent MI on	Primary: Atorvastatin led to a significant 37% reduction in the RR of the primary endpoint compared to placebo (95% CI, 17 to 52; P=0.001). Secondary: Atorvastatin led to a significant 27% reduction in the RR of all-cause mortality compared to placebo (95% CI, 1 to 48; P=0.059).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo All patients were randomized after a 6 week placebo lead in period.	≤600 mg/dL and ≥1 other CHD risk factor		annual ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) Secondary: All-cause mortality, acute hospital-verified cardiovascular endpoint (major cardiovascular disease events, angina, TIA, peripheral vascular disease requiring hospitalization or surgery), reduction in coronary revascular-ization, lipid reduction	Atorvastatin led to a significant 32% reduction in the RR of any cardiovascular endpoint compared to placebo (95% CI, 15 to 45; P=0.001). Atorvastatin was associated with a significant reduction in stroke compared to placebo (1.5 vs 2.8%; HR, 0.52; 95% CI, 0.31 to 0.89). Atorvastatin was not associated with a significant reduction in coronary revascularization compared to placebo (HR, 0.69; 95% CI, 0.41 to 1.16). Atorvastatin was associated with a significant 40% reduction in baseline LDL-C compared to placebo (P<0.0001). Atorvastatin was associated with a significant 26% reduction in baseline TC levels compared to placebo (P<0.0001). Atorvastatin was associated with a significant one percent increase in baseline HDL-C compared to placebo (P=0.0002). Atorvastatin was associated with a significant 36% reduction in baseline non-HDL-C compared to placebo (P<0.0001). Atorvastatin was associated with a significant 19% reduction in baseline TG compared to placebo (P<0.0001). Atorvastatin was associated with a significant 23% reduction in baseline apo B compared to placebo (P<0.0001). The frequency of adverse events was similar between the two treatments (P value not reported).
Neil et al.[137] (2006) CARDS Atorvastatin 10 mg/day vs	Post hoc analysis of CARDS Adult patients with type 2 diabetes without a history of CHD, LDL-C ≤160	N=2,838 3.9 years	Primary: Major cardiovascular events (acute CHD death, nonfatal MI, including silent MI on annual	Primary: Atorvastatin led to a significant 38% reduction in the RR of the primary endpoint in patients ≥65 years of age (95% CI, 8 to 58; ARR, 3.9%, P=0.017). Consequently, 21 patients would need to be treated for four years to prevent one major cardiovascular event. Atorvastatin led to a significant 37% reduction in the RR of the primary endpoint in patients <65 years of age (95% CI, 7 to 57; ARR, 2.7%; P=0.019).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo All patients were randomized after a 6 week placebo lead in period.	mg/dL, TG ≤600 mg/dL and ≥1 other CHD risk factor; stratified by age (≥65 years of age)		ECG, fatal or nonfatal stroke, resuscitated cardiac arrest and coronary revascularization procedures) among patients ≥65 and <65 years of age Secondary: All-cause mortality, acute hospital-verified cardiovascular endpoint (major cardiovascular disease events, angina, TIA, peripheral vascular disease requiring hospitalization or surgery) among patients ≥65 and <65 years of age	Consequently, 33 patients would need to be treated for four years to prevent one major cardiovascular event. Secondary: There was no significant effect on all-cause mortality in either the <65 (P=0.98) or the ≥65 year old population (P=0.245). Atorvastatin led to a significant reduction in LDL-C among both the younger and the older patients compared to placebo (38 and 41%, respectively; P<0.001). Atorvastatin led to a significant reduction in TC among both the younger and the older patients compared to placebo (26 and 27%, respectively; P<0.001). Atorvastatin led to a significant reduction in TG among both the younger and the older patients compared to placebo (P<0.001). The frequency of adverse events was similar between the two treatments (P value not reported).
Hitman et al.[138] (2007) CARDS Atorvastatin 10 mg/day vs	Subanalysis of CARDS Patients 40 to 75 years of age with type 2 diabetes without a history of CHD, LDL-C	N=2,838 3.9 years	Primary: Fatal or nonfatal stroke, type of stroke, risk factors for stroke Secondary:	Primary: Atorvastatin was associated with a significant 48% reduction in stroke compared to placebo (1.5 vs 2.5%; HR, 0.52; 95% CI, 0.31 to 0.89; P=0.016). Atorvastatin was associated with a significant 50% reduction in non-hemorrhagic stroke compared to placebo (1.1 vs 2.2%; HR, 0.50; 95% CI, 0.27 to 0.91; P=0.024).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo All patients were randomized after a 6 week placebo lead in period.	≤160 mg/dL, TG ≤600 mg/dL and ≥1 other CHD risk factor		Not reported	Atorvastatin was associated with a significant 42% reduction in stroke or TIAs compared to placebo (2.1 vs 3.6%; HR, 0.58; 95% CI, 0.37 to 0.92; P=0.019). Independent risk factors predicting stroke were age (HR, 2.3; P<0.001), microalbuminuria (HR, 2.0; P=0.007) and glycemic control (HR, 2.7; P=0.007). Women were at a lower risk for stroke than men (HR, 0.3; P=0.004). Secondary: Not reported
Sever et al.[139] (2003) ASCOT-LLA Atorvastatin 10 mg/day vs placebo All patients received antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach SBP and DBP goals of <140 and 90 mm Hg, respectively).	DB, MC, RCT Patients 40 to 79 years of age with either untreated or treated HTN, TC ≤6.5 mmol/L and not currently taking a statin or a fibrate; patients were also required to have >3 of the following cardiovascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes type 2, PAD, previous stroke or TIA, age >55 years, microalbuminuria or proteinuria, male sex, smoking,	N=10,305 3.3 years	Primary: Combined endpoint of nonfatal MI and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal heart failure, fatal and nonfatal stroke, total coronary endpoints, total cardiovascular events and procedures	Primary: Atorvastatin was associated with a significant 36% reduction in the primary endpoint compared to placebo (HR, 0.64; 95% CI, 0.50 to 0.83; P=0.0005). Secondary: Atorvastatin was associated with a significant 38% reduction in the primary endpoint, excluding silent MIs, compared to placebo (HR, 0.62; 95% CI, 0.47 to 0.81; P=0.0005). Atorvastatin was not associated with a significant reduction in all-cause mortality (P=0.1649), cardiovascular mortality (P=0.5066) or fatal and nonfatal heart failure (P=0.5794) compared to placebo. Atorvastatin was associated with a significant 27% reduction in the risk for fatal and nonfatal strokes compared to placebo (HR, 0.73; 95% CI, 0.56 to 0.96; P=0.0236). Atorvastatin was associated with a significant 29% reduction in the risk for total coronary events compared to placebo (HR, 0.71; 95% CI, 0.59 to 0.86; P=0.005). Atorvastatin was associated with a significant 21% reduction in the risk for total cardiovascular events and procedures compared to placebo (HR, 0.79; 95% CI, 0.69 to 0.90; P=0.0005).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	TC:HDL-C >6 or family history of CHD			
Sever et al[140] (2005) ASCOT-LLA Atorvastatin 10 mg/day vs placebo All patients received antihypertensive treatment (amlodipine or atenolol with additional therapy as needed to reach SBP and DBP goals of <140 and 90 mm Hg, respectively).	2 year extension of ASCOT-LLA Patients 40 to 79 years of age with either untreated or treated HTN, TC ≤6.5 mmol/L and not currently taking a statin or a fibrate; patients were also required to have >3 of the following cardio-vascular disease risk factors: left-ventricular hypertrophy, ECG abnormality, diabetes type 2, PAD, previous stroke or TIA, age >55 years, microalbuminuria or proteinuria, male sex, smoking, TC:HDL-C >6 or family history of CHD	N=10,305 5.5 years	Primary: Combined endpoint of nonfatal MI and fatal CHD Secondary: The primary outcome without silent events, all-cause mortality, total cardiovascular mortality, fatal and nonfatal stroke, fatal and nonfatal heart failure, total coronary endpoints, total cardiovascular events	Primary: Atorvastatin was associated with a significant 36% reduction in the primary endpoint compared to placebo (HR, 0.64; 95% CI, 0.53 to 0.78; P≤0.0001). Secondary: Atorvastatin was associated with a significant 37% reduction in the primary endpoint, excluding silent MIs, compared to placebo (HR, 0.63; 95% CI, 0.51 to 0.77; P≤0.0001). Atorvastatin was associated with a significant 15% reduction in the risk for all-cause mortality compared to placebo (HR, 0.85; 95% CI, 0.74 to 0.98; P=0.0219). Atorvastatin was not associated with a significant reduction in cardiovascular mortality (P=0.1281), or fatal and nonfatal heart failure (P=0.9809) compared to placebo. Atorvastatin was associated with a significant 23% reduction in the risk for fatal and nonfatal strokes compared to placebo (HR, 0.77; 95% CI, 0.63 to 0.95; P=0.0127). Atorvastatin was associated with a significant 27% reduction in the risk for total coronary events compared to placebo (HR, 0.73; 95% CI, 0.63 to 0.85; P≤0.0001). Atorvastatin was associated with a significant 19% reduction in the risk for total cardiovascular events and procedures compared to placebo (HR, 0.81; 95% CI, 0.73 to 0.89; P≤0.0001).
Downs et al.[141] (1998) AFCAPS/TexCAPS	DB, MC, PC, RCT Men 45 to 73	N=6,605 5.2 years	Primary First acute major coronary event (fatal or	Primary After an average follow up of 5.2 years, lovastatin was associated with a significant 37% lower incidence of the first acute major coronary event compared to placebo (95% CI, 0.50 to 0.79; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Lovastatin 20 to 40 mg QD vs placebo	years of age and postmenopausal women 55 to 73 years of age on a low-saturated fat, low-cholesterol diet with TC 180 to 264 mg/dL, LDL-C 130 to 190 mg/dL, HDL ≤45 mg/dL for men or ≤47 mg/dL for women and TG ≤400 mg/dL, without a prior history of MI, angina, claudication, cerebrovascular accident or TIA; patients with LDL-C 125 to 129 mg/dL were included when TC:HDL-C >6		nonfatal MI, unstable angina or sudden cardiac death) Secondary Fatal or nonfatal coronary revascularization procedure, unstable angina, fatal or nonfatal MI, fatal or nonfatal cardiovascular events, fatal or nonfatal coronary events, cardiovascular mortality and CHD mortality, total mortality, fatal and nonfatal cancer, safety, discontinuation rates	Secondary Lovastatin was associated with a significant 33% reduction in revascularization (95% CI, 0.52 to 0.85; P=0.001), 32% reduction in unstable angina (95% CI, 0.49 to 0.95; P=0.02), 40% reduction in the incidence of fatal or nonfatal MI (95% CI, 0.43 to 0.83; P=0.002), 25% reduction in fatal or nonfatal cardiovascular events (95% CI, 0.62 to 0.91; P=0.003) and 25% reduction in fatal or nonfatal coronary events (95% CI, 0.61 to 0.92; P=0.006) compared to placebo. There were too few events to perform survival analysis on cardiovascular (1.0 vs 1.4%) and CHD mortality (0.6 vs 0.8%) events based on prespecified criteria. The overall mortality rate and fatal and nonfatal cancer rates were similar between the two treatments (P value not reported). Discontinuation rates due to adverse events were 13.6 and 13.8% with lovastatin and placebo (P value not reported). Both treatments had similar rates of serious adverse events (34.2 vs 34.1%; P value not reported).
Schouten et al.[142] (2009) DECREASE III Fluvastatin XL 80 mg QD prior to surgery	RCT, DB, PC Patients ≥40 years of age who were scheduled for noncardiac vascular surgery (abdominal	N=497 ≥30 days post-surgery	Primary: Occurrence of myocardial ischemia Secondary: Composite of death from	Primary: Myocardial ischemia occurred in 10.8% of patients in the fluvastatin XL group within 30 days after surgery compared to 19.0% of patients in the placebo group (HR, 0.55; 95% CI, 0.34 to 0.88; P=0.01). The number of patients who would need to be treated to prevent 1 patient from having myocardial ischemia was 12. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo Patients in both groups also received beta-blocker therapy prior to surgery	aortic aneurysm repair, distal aortoiliac reconstruction, lower-limb arterial reconstruction, or carotid-artery endarterectomy) who were statin naïve		cardiovascular causes and nonfatal MI	The composite of death from cardiovascular causes or nonfatal myocardial infarction occurred in 4.8% of patients receiving fluvastatin XL compared to 10.1% of patients receiving placebo (HR, 0.47; 95% CI, 0.24 to 0.94; P=0.03). The number of patients who would need to be treated to prevent the composite end point of death from cardiovascular causes or nonfatal MI in one patient was 19.
No authors listed.[143] (2002) ALLHAT-LLT Pravastatin 40 mg/day vs usual care Vigorous cholesterol-lowering therapy in the usual care group was discouraged.	MC, OL, RCT Patients ≥55 years of age, with Stage 1 or 2 HTN, ≥1 additional CHD risk factor, fasting LDL-C 120 to 189 mg/dL for patients with no known CHD or 100 to 129 mg/dL for patients with known CHD and fasting TG <350 mg/dL	N=10,355 Mean, 4.8 years (maximum 7.8 years)	Primary: All-cause mortality Secondary: Composite of fatal CHD or nonfatal MI, cause-specific mortality, total and site-specific cancers	Primary: All-cause mortality did not differ significantly between the two treatments (RR, 0.99; 95% CI, 0.89 to 1.11; P=0.88). Secondary: Rates of CHD (fatal CHD plus nonfatal MI) and stroke were slightly lower with pravastatin compared to usual care (RR, 0.91; 95% CI, 0.79 to 1.04; P=0.16). There were 209 total strokes with pravastatin and 231 total strokes with usual care (RR, 0.91; 95% CI, 0.75 to 1.09; P=0.31). Heart failure rates were similar between the two treatments (RR, 0.99; 95% CI, 0.83 to 1.18; P=0.89). The six year cancer rates were similar between the two treatments (RR, 1.03; 95% CI, 0.89 to 1.19; P=0.66).
Nakamura et al[144] (2006) MEGA Pravastatin 10 to 20 mg/day plus NCEP step I diet	OL, PRO, RCT Patients 40 to 70 years of age weighing ≥40 kg, with hypercholesterole mia, without a	N=8,214 Mean 5.2 years	Primary: CHD incidence, sudden cardiac deaths, MIs, coronary re-vascularization Secondary:	Primary: Pravastatin plus diet was associated with a significant reduction in the incidence of CHD compared to diet (3.3 vs 5.0%; HR, 0.67; 95% CI, 0.49 to 0.91; P=0.01). There was no significant difference between the two treatments in the incidence of sudden cardiac deaths or anginal episodes (P>0.05 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs NCEP step I diet	history of CHD or FH		CHD and cerebral infarction, all cardiovascular events, strokes, all-cause mortality	Secondary: Pravastatin plus diet was associated with a significant reduction in the incidence of MIs compared to diet (0.9 vs 1.6%; HR, 0.52; 95% CI, 0.29 to 0.94; P=0.03). Pravastatin plus diet was associated with a significant reduction in the incidence of coronary revascularizations compared to diet (2.0 vs 3.2%; HR, 0.60; 95% CI, 0.41 to 0.89; P=0.01). Secondary: Pravastatin plus diet was associated with a significant reduction in the incidence of CHD and cerebral infarctions compared to diet (5.0 vs 7.1%; HR, 0.70; 95% CI, 0.54 to 0.90; P=0.005). Pravastatin plus diet was associated with a significant reduction in the incidence of all cardiovascular events compared to diet (6.4 vs 8.5%; HR, 0.74; 95% CI, 0.59 to 0.94; P=0.01). There was no significant difference between the two treatments in all-cause mortality or the incidence of strokes (P>0.05 for both).
No authors listed.[145] (1993) PMS-CRP Pravastatin 20 to 40 mg/day vs placebo	DB, MC, PC, RCT Adult patients with hypercholesterolemia	N=1,062 26 weeks	Primary: Lipid levels at 13 and 26 weeks, occurrence of cardiovascular events Secondary: Not reported	Primary: After 13 weeks, pravastatin was associated with significant reductions in LDL-C (26%), TC (19%) and TG (12%) and significant elevations in HDL-C (7%) compared to placebo (P<0.001 for all). Throughout the 26 weeks, there were no differences in the total incidence of clinical adverse events between the two treatments. No MIs or cerebral infarctions occurred with pravastatin, and a total of six MIs and three cerebral infarctions occurred with placebo (P value not reported). Secondary: Not reported
Shepherd et al.[146] (1995) WOSCOPS Pravastatin 40	DB, PC Men 45 to 64 years of age with hypercholesterole	N=6,595 4.9 years	Primary: Incidence of nonfatal MI or death from CHD as a first	Primary: Pravastatin was associated with a significant 31% reduction in the risk of the combined primary endpoint of definite nonfatal MI and death from CHD (95% CI, 17 to 43; P<0.001) compared to placebo. The absolute difference in the risk at five-years was 2.4%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day vs placebo	mia and no history of MI		event Secondary: Incidence of death from CHD and nonfatal MI	 Secondary: The reduction in the risk of nonfatal MI with pravastatin was significant whether the definite cases of MI were considered alone or in combination with suspected cases (P≤0.001). In the analysis of both definite and suspected cases of death from CHD, there was a significant risk reduction of 33% with pravastatin (95% CI, 1 to 55; P=0.042), but not in the analysis of definite cases alone (P value not reported). When the effect of pravastatin on death from all cardiovascular causes was analyzed, a 32% risk reduction was observed (95% CI, 3 to 53; P=0.033). Additionally, pravastatin was associated with a significant 31% reduction in the frequency of coronary angiography (95% CI, 10 to 47; P=0.007) and a 37% reduction in the frequency of revascularization procedures (95% CI, 11 to 56; P=0.009) compared to placebo.
Ford et al.[147] (2007) WOSCOPS Pravastatin 40 mg/day vs placebo	ES of WOSCOPS Men 45 to 64 years of age with hypercholesterolemia and no history of MI	N=6,595 15 years of total follow-up	Primary: Mortality from CHD or nonfatal MI, CHD, cardiovascular causes, all-cause mortality Secondary: Not reported	Primary: Pravastatin was associated with a significant reduction in the risk of death from CHD or nonfatal MI compared to placebo over a 15 year period (11.8 vs 15.5%; HR, 0.73; 95% CI, 0.63 to 0.83; P<0.001). Pravastatin was associated with a significant reduction in the risk of death from all causes compared to placebo over a 15 year period (18.7 vs 20.5%; HR, 0.88; 95% CI, 0.79 to 0.99; P=0.03). Pravastatin was associated with a significant reduction in the risk of death from cardiovascular causes compared to placebo over a 15 year period (7.6 vs 9.0%; HR, 0.81; 95% CI, 0.68 to 0.96; P=0.01). Pravastatin was associated with a significant reduction in the risk of death from CHD compared to placebo over a 15 year period (5.1 vs 6.3%; HR, 0.78; 95% CI, 0.64 to 0.96; P=0.02). Pravastatin was associated with a small increase in the risk of death from stroke compared to placebo over a 15 year period (1.6 vs 1.1%; HR, 1.37; 95% CI, 0.90 to 2.09; P=0.14).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Secondary: Not reported
Ridker et al.[148] (2008) JUPITER Rosuvastatin 20 mg/day vs placebo	DB, MC, PC, RCT Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL	N=17,802 1.9 years	Primary: Incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial re-vascularization procedure or confirmed death from cardiovascular causes) Secondary: Individual components of the primary endpoint, all-cause mortality	Primary: At the time of trial termination (median follow up, 1.9 years; maximal follow up, 5.0 years), 142 first major cardiovascular events had occurred with rosuvastatin compared to 251 first major cardiovascular events with placebo. The rates of the primary endpoint were 0.77 and 1.36 per 100 persons-years of follow up with rosuvastatin and placebo, respectively (HR for rosuvastatin, 0.56; 95% CI, 0.46 to 0.69; P<0.00001). The number of patients who would need to be treated with rosuvastatin for two years to prevent the incidence of one primary endpoint is 95, and the NNT for four years is 31. Secondary: Rosuvastatin was associated with significant reductions in rates of the individual components of the primary endpoint. The corresponding rates per 100 persons-years of follow up for the individual endpoints with rosuvastatin and placebo were: 0.17 and 0.37 for fatal or nonfatal MI (HR, 0.46; 95% CI, 0.30 to 0.70; P=0.0002); 0.18 and 0.34 for fatal or nonfatal stroke (HR, 0.52; 95% CI, 0.34 to 0.79; P=0.002); 0.41 and 0.77 for revascularization or unstable angina (HR, 0.53; 95% CI, 0.40 to 0.70; P<0.00001) 0.45 and 0.85 for the combined endpoint of MI, stroke or death from cardiovascular causes (HR, 0.53; 95% CI, 0.40 to 0.69; P<0.00001) and 1.00 and 1.25 for death from any cause (HR, 0.80; 95% CI, 0.67 to 0.97; P=0.02). In analyses limited to deaths for which the date of death was known with certainty, there was a similar reduction in the HR associated with rosuvastatin (0.81; 95% CI, 0.67 to 0.98; P=0.03). For patients with elevated hsCRP levels but no other major risk factor other than increased age, the benefit of rosuvastatin was similar to that for higher risk patients (HR, 0.63; 95% CI, 0.44 to 0.92; P=0.01).
Everett et al[149] (2001) JUPITER	Post hoc analysis of JUPITER Men ≥50 years of	N=17,802 1.9 years (maximum, 5.0	Primary: Incidence of stroke	Primary: At the time of trial termination, 33 and 64 strokes occurred in patients receiving rosuvastatin and placebo. Rosuvastatin resulted in a 48% reduction in the HR of fatal and nonfatal stroke compared to placebo (incidence rate,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Rosuvastatin 20 mg/day vs placebo	age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL	years)	Secondary: Not reported	0.18 vs 0.34 per 100 person-years; HR, 0.52; 95% CI, 0.34 to 0.79; P=0.002), a finding that was consistent across all examined subgroups. This finding was due to a 51% reduction in the rate of ischemic stroke (HR, 0.49; 95% CI, 0.30 to 0.81; P=0.004), with no difference in the rates of hemorrhagic stroke (HR, 0.67; 95% CI, 0.24 to 1.88; P=0.44). TIAs were observed with similar frequency in the two treatments (HR, 0.93; 95% CI, 0.56 to 1.56; P=0.79). The projected NNT for five-years to prevent one stroke was 123. Secondary: Not reported
Koenig et al[150] (2001) JUPITER Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL; patients with high global cardiovascular risk (10 year Framingham risk score >20% and 10 year European systematic coronary risk evaluation ≥5%)	N=17,802 (9 and 52% were considered to be high risk based on 10 year Framingham risk score and 10 year European systematic coronary risk evaluation) 1.9 years (maximum, 5.0 years)	Primary: Incidence of first MI, stroke or cardiovascular death; first incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure or confirmed death from cardiovascular causes); all-cause mortality Secondary: Not reported	Primary: Patients with a 10 year Framingham risk score >20% the rate of the combined endpoint of MI, stroke or cardiovascular death was 9.4 and 18.2 per 1,000 person-years with rosuvastatin and placebo (HR, 0.50; 95% CI, 0.27 to 0.93; P=0.028). Rosuvastatin had no significant effect on the incidence of major cardiovascular events (P=0.155) and all-cause mortality (P=0.193). Among patients with a 10 year European systematic coronary risk evaluation ≥5%, the corresponding rates were 6.9 vs 12.0 using a model extrapolating risk for age ≥65 years (HR, 0.57; 95% CI, 0.43 to 0.78; P=0.0003) and rates were 5.9 vs 12.7 when risk for age was capped at 65 years of age (HR, 0.47; 95% CI, 0.32 to 0.68; P<0.0001). Rosuvastatin significantly reduced the incidence of major coronary events (P=0.0003) but not all-cause mortality (P=0.076) in patients with a 10 year European systematic coronary risk evaluation ≥5% extrapolating risk for age ≥65 years. When the risk for age was capped at 65 years of age, rosuvastatin had significant effect on the incidence of major cardiovascular events (P<0.0001) and all-cause mortality (P=0.022). Secondary: Not reported
Ridker et al[151]	Post hoc analysis	N=17,802	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2010) JUPITER Rosuvastatin 20 mg/day vs placebo	of JUPITER Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500 mg/dL; stratified by kidney function (eGFR <60 mL/min and eGFR ≥60 mL/min)	(n=3,267 with moderate CKD) 1.9 years (maximum, 5.0 years)	Incidence of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure or confirmed death from cardiovascular causes), all-cause mortality Secondary: Individual components of the primary endpoint, all-cause mortality	Among patients with eGFR <60 mL/min, the incidence rate of the primary endpoint was significantly lower with rosuvastatin compared to placebo (incidence rate, 1.08 vs 1.95 per 100 person-years; HR, 0.55; 95% CI, 0.38 to 0.82; P=0.002). Irrespective of treatment, at trial end 111 and 282 patients with eGFR <60 and ≥60 mL/min suffered a primary endpoint (incidence rate, 1.51 vs 0.95 per 100 person-years; HR, 1.54; 95% CI, 1.23 to 1.92; P=0.0002). Secondary: Among patients with eGFR <60 mL/min, rosuvastatin significantly reduced the rate of MI (incidence rate, 0.21 vs 0.54 per 100 person-years; HR, 0.40; 95% CI, 0.17 to 0.90; P=0.02), arterial revascularization (0.51 vs 1.07; HR, 0.48; 95% CI, 0.28 to 0.83; P=0.006), the combined MI, stoke or confirmed cardiovascular death (0.64 vs 1.09; HR, 0.59; 95% CI, 0.36 to 0.99; P=0.04), venous thromboembolism (0.16 vs 0.46; HR, 0.14 to 0.88; P=0.02), all-cause mortality (0.85 vs 1.53; HR, 0.56; 95% CI, 0.37 to 0.85; P=0.005), combined primary endpoint plus any death (1.72 vs 3.13; HR, 0.55; 95% CI, 0.41 to 0.75; P=0.0001) and the primary endpoint plus VTE plus any death (1.86 vs 3.51; HR, 0.53; 95% CI, 0.40 to 0.71; P<0.0001) compared to placebo. Among patients with eGFR <60 mL/min, rosuvastatin demonstrated no benefit compared to placebo in reducing the risk of stroke (incidence rate, 0.27 vs 0.38 per 100 person-years; HR, 0.71; 95% CI, 0.31 to 1.59; P=0.40).
Ridker et al.[152] (2009) JUPITER Rosuvastatin 20 mg/day vs placebo	Post hoc analysis of JUPITER Men ≥50 years of age and women ≥60 years of age with no known history of cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L and TG <500	N=17,802 1.9 years (maximum, 5 years)	Primary: Incidence of a first major cardiovascular event Secondary: Not reported	Primary: For the endpoint of MI, stroke, revascularization or death, the five-year NNT was 20 (95% CI, 14 to 34). All subgroups had five-year NNTs for this combined endpoint below 50 (men, 17; women, 31; whites, 21; nonwhites, 19; BMI ≤25 kg/m^2, 18; BMI >25 kg/m^2, 21; with or without a family history of coronary disease, 9 and 6; with or without metabolic syndrome, 19 and 22; estimated 10 years Framingham risk >10% and <10%, 14 and 37). For the combined primary endpoint plus VTE, the five-year NNT was 18 (95%; 13 to 29). For the endpoint of MI, stroke or death, the five-year NNT was 29 (95% CI, 19 to 56).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	mg/dL			In sensitivity analyses addressing the theoretical utility of alternative agents, five-year NNT values of 38 and 57 were estimated for statin regimens that deliver 75 and 50% of the relative benefit observed in JUPITER, respectively. Secondary: Not reported
Taylor et al.[153] (2011) Statins vs placebo or usual care	SR (14 RCTs) Patients ≥18 years of age with no restrictions on TC, LDL-C or HDL-C levels, population had ≤10% of patients with a previous history of cardiovascular disease	N=34,272 ≥12 months	Primary: All-cause mortality; fatal and nonfatal CHD; cardiovascular disease and stroke events; combined endpoint of fatal and non fatal CHD, cardiovascular disease and stroke Secondary: Change from baseline in TC, revascularization, adverse events, quality of life	Primary: None of the individual trials (eight) showed strong evidence of a reduction in all-cause mortality, but pooled analysis demonstrated that statins were associated with a significant 16% decrease in all-cause mortality (RR, 0.84; 95% CI, 0.79 to 0.96). Four trials demonstrated a significant reduction in the combined endpoint of fatal and nonfatal CHD in favor of statins (RR, 0.72; 95% CI, 0.65 to 0.79). Six trials demonstrated a significant reduction in combined endpoint of fatal and nonfatal cardiovascular disease in favor of statins (RR, 0.74; 95% CI, 0.66 to 0.85). Seven trials demonstrated a significant reduction in stroke events in favor of statins (RR, 0.78; 95% CI, 0.65 to 0.94). Three trials demonstrated a significant reduction in the combined endpoint of fatal and nonfatal CHD, cardiovascular disease and stroke in favor or statins (RR, 0.70; 95% CI, 0.61 to 0.79). Secondary: Five trials demonstrated a significant reduction in revascularization in favor of statins (RR, 0.66; 95% CI, 0.53 to 0.83). Nine and 11 trials reported on TC and LDL-C, demonstrating significant reductions in both with a statin (0.89 mmol/L [95% CI, -1.20 to -0.57] and 0.92 [95% CI, -1.10 to -0.74]). In terms of adverse events, incidence rates indicated no difference between statins and control groups (RR, 0.99; 95% CI, 0.94 to 1.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				There was no reliable data on patient quality of life.
Mora et al.[154] (2010) Statin therapy vs placebo	MA (5 primary prevention statin RCTs) Women receiving statin therapy	N=not reported Duration not reported	Primary: Cardiovascular disease, all cause mortality Secondary: Not reported	Primary: Compared to placebo, statin therapy in women significantly reduced cardiovascular disease by about one third in exclusively primary prevention trials. The summary RR for the three trials was 0.63 (95% CI, 0.49 to 0.82; P<0.001). When trials that included predominately primary prevention were analyzed together with the exclusively primary prevention trials, the summary RR was similar but no significant (0.79; 95% CI, 0.59 to 1.05; P=0.11). When two additional trials were included that did not report sex specific outcomes for women, the summary RR was unchanged (0.82; 95% CI, 0.69 to 0.98; P=0.03). The summary RR for the three exclusively primary prevention trials (n=13,154 women; 216 deaths) that reported sex specific total mortality was 0.78 (95% CI, 0.53 to 1.15; P=0.21). When all trials that reported sex specific mortality outcomes in predominantly or exclusively primary prevention in women were included, the summary RR was similar. Secondary: Not reported
Baigent et al.[155] (2005) Statins (pravastatin 40 mg/day, fluvastatin 40 to 80 mg/day, simvastatin 20 to 40 mg/day, atorvastatin 10 mg/day, lovastatin 20 to 80 mg/day) vs	MA (14 RCTs) Demographics not reported	N=90,056 ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality Secondary: Effect on CHD death and on major coronary events (nonfatal MI or CHD death) in prespecified subgroups; effect on stroke,	Primary: Statin therapy was associated with a significant 12% reduction in all-cause mortality per 1 mmol/L reduction in LDL-C compared to placebo (RR, 0.88; 95% CI, 0.84 to 0.91; P<0.0001). Statin therapy was associated with a significant 19% reduction in CHD mortality compared to placebo (3.4 vs 4.4%; RR, 0.81; 95% CI, 0.76 to 0.85; P<0.0001). Statin therapy was associated with a nonsignificant 17% reduction in non-CHD mortality compared to placebo (1.2 vs 1.3%; RR, 0.93; 95% CI, 0.83 to 1.03; P value not reported). Secondary: Statin therapy was associated with a significant 17% reduction in vascular mortality compared to placebo (4.7 vs 5.7%; RR, 0.83; 95% CI, 0.79 to 0.87;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
placebo			cancer, and vascular procedures, vascular events	P<0.0001). Statin therapy was associated with a significant 21% reduction in major vascular events compared to placebo (RR, 0.79; 95% CI, 0.77 to 0.81; P<0.0001). Statin therapy was associated with a significant 26% reduction in nonfatal MI compared to placebo (RR, 0.74; 99% CI, 0.70 to 0.79; P<0.0001). Statin therapy was associated with a significant 23% reduction in any major coronary event compared to placebo (RR, 0.77; 95% CI, 0.74 to 0.80; P<0.0001). Statin therapy was associated with a significant 24% reduction in any coronary revascularization compared to placebo (RR, 0.76; 95% CI, 0.73 to 0.80; P<0.0001). Statin therapy was associated with a significant 21% reduction in any stroke compared to placebo (RR, 0.79; 95% CI, 0.77 to 0.81; P<0.0001). Statin therapy was associated with a nonsignificant increase in the incidence of rhabdomyolysis compared to placebo (P=0.4).
No authors listed.[156] (2008) CTT Collaborators Statins (pravastatin 40 mg/day, fluvastatin 40 to 80 mg/day, simvastatin 20 to 40 mg/day, atorvastatin 10 mg/day, lovastatin	MA, subanalysis (14 trials) Demographics not reported	N=90,056 ≥2 years	Primary: All-cause mortality, CHD mortality, non-CHD mortality among diabetes and non-diabetes patients Secondary: Effect on CHD death and on major coronary events (nonfatal	Primary: Among patients with diabetes, statins were associated with a significant nine percent reduction in all-cause mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.91; 99% CI, 0.82 to 1.01; P=0.02). Among patients without diabetes, statins were associated with a significant 13% reduction in all-cause mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.87; 99% CI, 0.82 to 0.92; P<0.0001). Secondary: Among patients with diabetes, statins were associated with a significant 13% reduction in vascular mortality per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.87; 99% CI, 0.76 to 1.00; P=0.008) and no effect on nonvascular mortality (RR, 0.97; 99% CI, 0.82 to 1.16; P=0.7).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
20 to 80 mg/day) vs placebo			MI or CHD death), major vascular events among diabetic and non-diabetic patients	Among patients with diabetes, statins were associated with a significant 21% reduction in major vascular events per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.79; 99% CI, 0.72 to 0.86; P<0.0001). Among patients without diabetes, statins were associated with a significant 21% reduction in major vascular events per each additional mmol/L reduction in LDL-C compared to placebo (RR, 0.79; 99% CI, 0.76 to 0.82; P<0.0001). Among patients with diabetes, statins were associated with a significant 22% reduction in MI or coronary death (RR, 0.78; 99%CI, 0.69 to 0.87; P<0.0001), 25% reduction in coronary revascularization (RR, 0.75; 99% CI, 0.64 to 0.88; P<0.0001) and 21% reduction in stroke (RR, 0.79; 99% CI, 0.67 to 0.93; P=0.0002) compared to placebo. After five-years of treating 1,000 diabetic patients with statin therapy, 42 patients may be prevented from having a major vascular event (95% CI, 30 to 55; P value not reported). The benefit was greater among patients with diabetes and known vascular disease at baseline.
O'Regan et al.[157] (2008) Statins (atorvastatin 10 to 80 mg/day, simvastatin 20 to 40 mg/day, fluvastatin 40 to 80 mg/day, pravastatin 10 to 40 mg/day, lovastatin 20 to 73 mg/day) vs placebo	MA (41 primary prevention trials, 1 secondary prevention trial) Demographics not reported	N=121,285 Up to 6 years	Primary: All-cause mortality, all-stroke incidence Secondary: Incidence of cardiovascular deaths, non-hemorrhagic cerebrovascular events, hemorrhagic strokes, fatal strokes	Primary: Compared to placebo, statin therapy was associated with a significant reduction in the risk of all-cause mortality (RR, 0.88; 95% CI, 0.83 to 0.93). Compared to placebo, statin therapy was associated with a significant reduction in the risk of strokes (RR, 0.84; 95% CI, 0.79 to 0.91). Secondary: Compared to placebo, statin therapy was associated with a significant reduction in the risk of cardiovascular death (RR, 0.81; 95% CI, 0.74 to 0.90). Compared to placebo, statin therapy was associated with a significant reduction in the risk of nonhemorrhagic cerebrovascular events (RR, 0.81; 95% CI, 0.69 to 0.94). Compared to placebo, statin therapy was associated with a nonsignificant reduction in the risk hemorrhagic strokes (RR, 0.94; 95% CI, 0.68 to 1.30). Compared to placebo, statin therapy was associated with a nonsignificant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				reduction in the risk of fatal strokes (RR, 0.99; 95% CI, 0.80 to 1.21). A meta-regression analysis determined that every unit increase in LDL-C was associated with a 0.3% increased risk of mortality (RR, 1.003; 95% CI, 1.0005 to 1.006; P=0.02).
Secondary Prevention of Coronary Heart Disease (Single-Entity Agents)				
Bushnell et al.[158] (2006) Statin therapy vs no statin therapy	MA Patients with CHD or vascular disease	N=22,943 90 days	Primary: Incidence of stroke at 90 days, stroke severity, mortality from strokes, differences between sexes Secondary: Not reported	Primary: Patients reporting statin therapy had lower rates of stroke at 90 days of follow up (HR, 0.72; 95% CI, 0.53 to 0.97; P value not reported). Statin therapy was not associated with a significant reduction in stroke mortality (P=0.8). Women had an increased risk of experiencing a severe stroke compared to men (P=0.035). Statin therapy was not associated with a significant reduction in stroke severity among women (P=0.096). Secondary: Not reported
LaRosa et al.[159] (2005) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	DB, MC, PG, RCT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=10,001 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Individual components of a major coronary event,	Primary: Compared to 10 mg, 80 mg was associated with a significant 22% reduction in the incidence of the primary endpoint (10.9 vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; P=0.0002). Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of strokes (3.1 vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.96; P=0.021). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events (5.0 vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; P=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% RRR in cerebrovascular events (P=0.002) and a 0.5% RRR in stroke (P=0.041).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, and any coronary event, side effects	Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of nonfatal MIs (6.2 vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; P=0.004). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of major coronary events (8.3 vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0019). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events (26.5 vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of hospitalization for heart failure (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). There was no significant difference between the two treatments in the incidence of death from CHD (3.3 vs 2.4%; HR, 0.74; 95% CI, 0.59 to 0.94; P=0.01). There was no significant difference between the two treatments in the incidence of resuscitation after cardiac arrest (0.5%; HR, 0.96; 95% CI, 0.56 to 1.67; P=0.89). There was no significant difference between the two treatments in the incidence of PAD (5.6 vs 5.5%; HR, 0.97; 95% CI, 0.83 to1.15; P=0.76). There was no significant difference between the two treatments in the incidence of death from any cause (5.6 vs 5.7%; HR, 1.01; 95% CI, 0.85 to 1.19; P=0.92). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of treatment-related adverse events (5.8 vs 8.1%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Compared to 10 mg, 80 mg was associated with a significantly higher incidence of ALT and AST elevations greater than three times the upper limit of normal (0.2 vs 1.2%; P<0.001).
Shah et al.[160] (2008) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Subanalysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease) with a previous CABG	N=4,654 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Safety	Primary: A first major cardiovascular event occurred in 11.4% (n=529) of patients with prior CABG and 8.5% (n=453) of those without prior CABG (HR, 1.38; 95% CI, 1.22 to 1.56; P<0.0001). Among post-CABG patients, a primary endpoint event occurred in 9.7 (n=224) vs 13.0% (n=305) of patients receiving 80 and 10 mg/day, resulting in a 27% RR reduction and a 3.3% ARR (HR, 0.73; 95% CI, 0.62 to 0.87; P=0.0004). During follow up, 11.3 (n=262) vs 15.9% (n=371) of patients receiving 80 and 10 mg/day underwent repeat coronary revascularization, either with CABG or percutaneous coronary intervention, resulting in a 30% RR reduction and a 4.6% ARR (HR, 0.70; 95% CI, 0.60 to 0.82; P<0.0001). The combined endpoint of a major cardiovascular event or coronary revascularization occurred in 18.0 (n=417) vs 24.2% (n=566) in patients receiving 80 and 10 mg/day, resulting in a 28% RR reduction and a 6.2% ARR (HR, 0.72; 95% CI, 0.64 to 0.82; P<0.0001). Secondary: In the CABG cohort, discontinuations from therapy due to treatment-related adverse events during the five-years of follow up occurred in 3.8 (n=87) vs 2.7% (n=62) of patients receiving 80 and 10 mg/day (P=0.004). Treatment-related myalgias were reported in 1.3% of patients receiving both treatments, and no post-CABG patient experienced an elevation of CK >10 times the upper limit of normal on two consecutive measurements. Elevated AST and ALT greater than three times the upper limit of normal on consecutive measurements occurred in 1.1 and 0.3% of patients receiving 80 and 10 mg/day (P=0.0003).
Waters et al.[161] (2006) TNT	Subanalysis of TNT Patients 35 to 75	N=10,001 5 years	Primary: First major cardiovascular event (death	Primary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of the primary endpoint (10.9 vs 8.7%; HR, 0.78; 95% CI, 0.69 to 0.89; P=0.0002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)		from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, any coronary event	Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of strokes (3.1 vs 2.3%; HR, 0.75; 95% CI, 0.59 to 0.86; P=0.021). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events (5.0 vs 3.9%; HR, 0.77; 95% CI, 0.64 to 0.93; P=0.007). Each 1 mg/dL reduction in LDL-C was associated with a 0.6% RR reduction in cerebrovascular events (P=0.002) and a 0.5% RR reduction in stroke (P=0.041). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of nonfatal MIs (6.2 vs 4.9%; HR, 0.78; 95% CI, 0.66 to 0.93; P=0.004). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of major coronary events (8.3 vs 6.7%; HR, 0.80; 95% CI, 0.69 to 0.92; P=0.0019). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events (26.5 vs 21.6%; HR, 0.79; 95% CI, 0.73 to 0.86; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events (33.5 vs 28.1%; HR, 0.81; 95% CI, 0.75 to 0.87; P<0.0001). There was no significant difference between the two treatments in the incidence of TIAs (P=0.099). There was no significant difference between the two treatments in the incidence of death from CHD (P=0.087). Compared to 10 mg, 80 mg was associated with a significantly higher incidence of treatment-related adverse events (5.8 vs 8.1%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				Compared to 10 mg, 80 mg was associated with a significantly higher incidence of ALT and AST elevations at least three times the upper limit of normal (0.2 vs 1.2%; P<0.001).
Deedwania et al.[162] (2006) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease), stratified by metabolic syndrome	N=5,584 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) among patients with metabolic syndrome Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, any coronary event among patients with metabolic syndrome	Primary: Compared to 10 mg, 80 mg was associated with a significant 29% reduction in the incidence of the primary endpoint among patient with metabolic syndrome (13.0 vs 9.5%; HR, 0.71; 95% CI, 0.61 to 0.84; P<0.0001). Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events among patients with metabolic syndrome (HR, 0.74; 95% CI, 0.59 to 0.93; P=0.011). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of major coronary events among patients with metabolic syndrome (HR, 0.72; 95% CI, 0.60 to 0.86; P=0.0004). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events among patients with metabolic syndrome (HR, 0.75; 95% CI, 0.67 to 0.83; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events among patients with metabolic syndrome (HR, 0.78; 95% CI, 0.71 to 0.85; P<0.0001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of hospitalization for CHF among patients with metabolic syndrome (HR, 0.73; 95% CI, 0.55 to 0.96; P=0.027). There was no significant difference between the two treatments in the incidence of all-cause mortality among patients with metabolic syndrome (P value not reported).
Shepherd et al.[163] (2006)	Post hoc analysis of TNT	N=1,501	Primary: First major	Primary: Compared to 10 mg, 80 mg was associated with a significant 25% reduction in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Patients 35 to 75 years of age with type 2 diabetes and CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	5 years	cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) among patients with type 2 diabetes Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, any coronary event among patients with type 2 diabetes	the incidence of the primary endpoint among patients with diabetes (17.9 vs 13.8%; HR, 0.75; 95% CI, 0.58 to 0.97; P=0.026). Secondary: Significant differences between the treatments in favor of 80 mg/day were observed for the secondary outcomes of time to cerebrovascular event (HR, 0.69; 95% CI, 0.48 to 0.98; P=0.037) and time to cardiovascular event (HR, 0.85; 95% CI, 0.73 to 1.00; P=0.044) There was no significant difference between the two treatments in the incidence of cerebrovascular events among patients with diabetes (P=0.437). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of nonfatal MI among patients with diabetes (HR, 0.79; 95% CI, 0.55 to 1.14; P=0.202). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of fatal and nonfatal stroke among patients with diabetes (HR, 0.67; 95% CI, 0.43 to 1.04; P=0.075). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from CHD among patients with diabetes (HR, 0.74; 95% CI, 0.47 to 1.18; P=0.203). There was no significant difference between the two treatments in the incidence of major coronary events among patients with diabetes (P=0.922). There was no significant difference between the two treatments in the incidence of any coronary events among patients with diabetes (P=0.192). There was no significant difference between the two treatments in the incidence of any cardiovascular events among patients with diabetes (P=0.458). There was no significant difference between the two treatments in the incidence of major cardiovascular events among patients with diabetes (P=0.689).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				There was no significant difference between the two treatments in the incidence of hospitalization with heart failure among patients with diabetes (P=0.277). There was no significant difference between the two treatments in the incidence of all-cause mortality among patients with diabetes (P=0.521). There was no significant difference between the two treatments in the incidence of PAD among patients with diabetes (P=0.789). There was no significant difference between the two treatments in the incidence of treatment-related adverse effects or persistent elevations in liver enzymes (P values not reported).
Wenger et al.[164] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients ≥65 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=3,809 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest or fatal or nonfatal stroke) Secondary: Individual components of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any	Primary: Compared to 10 mg, 80 mg was associated with a significant 19% reduction in the incidence of the primary endpoint among patients ≥65 years of age (12.6 vs 10.3%; HR, 0.81; 95% CI, 0.67 to 0.98; P=0.032). Consequently, in treating 35 patients with 80 mg vs 10 mg, one cardiovascular event could be prevented over a five-year period. Secondary: Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of cerebrovascular events among patients ≥65 years of age (P=0.010). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of nonfatal MI among patients ≥65 years of age (HR, 0.79; 95% CI, 0.60 to 1.03; P=0.084). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of fatal and nonfatal stroke among patients ≥65 years of age (HR, 0.79; 95% CI, 0.57 to 1.09; P=0.158). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from CHD among patients ≥65 years of age (HR, 0.91; 95% CI, 0.63 to 1.29; P=0.59).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			cardiovascular event, and any coronary event, side effects	Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of resuscitated cardiac arrests among patients ≥65 years of age (HR, 1.19; 95% CI, 0.49 to 2.87; P=0.70). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any cardiovascular events among patients ≥65 years of age (P<0.001). Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of any coronary events among patients ≥65 years of age (P<0.001). Compared to 10 mg, 80 mg was associated with a significant reduction in incidence of hospitalization for heart failure among patients ≥65 years of age (P=0.008). There was no significant difference between the two treatments in the incidence of major coronary events among patients ≥65 years of age (P=0.128). Compared to 10 mg, 80 mg was associated with a nonsignificant reduction in the incidence of death from cardiovascular causes among patients ≥65 years of age (HR, 0.91; 95% CI, 0.67 to 1.24; P=0.55). Compared to patients receiving 10 mg, more patients receiving 80 mg died from noncardiovascular causes among patients ≥65 years of age (HR, 1.26; 95% CI, 0.93 to 1.70; P=0.129). More patients ≥65 years of age receiving 80 mg experienced treatment-related adverse events compared to patients ≥65 years of age receiving 10 mg (P value not reported).
Khush et al.[165] (2007) TNT Atorvastatin 10 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either	N=10,001 5 years	Primary: Hospitalization for heart failure among patients with and without a	Primary: Prior history of heart failure is a significant risk factor for hospitalization from heart failure. While 14.1% of patients with heart failure at baseline were hospitalized for heart failure, only 1.9% of patients who did not have heart failure at baseline were hospitalized for heart failure during the trial period (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 80 mg/day	previous MI, coronary revascularization, angina with objective evidence of coronary disease)		history of heart failure Secondary: Not reported	Compared to 10 mg, 80 mg was associated with a significant reduction in the incidence of hospitalization from heart failure among patients with heart failure at baseline (17.3 vs 10.6%; HR, 0.59; 95% CI, 0.4 to 0.80; P=0.008). Mortality was significantly higher among patients with heart failure compared to patients without heart failure at baseline (15.0 vs 4.9%; P<0.001). Each reduction of 1 mg/dL in LDL-C was associated with a reduction in the risk of hospitalization for heart failure by 0.6% (P=0.007). Secondary: Not reported
LaRosa et al.[166] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease), stratified by LDL-C level	N=9,769 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with LDL-C <64 mg/dL (Quintile 1), 64 to ≤77 mg/dL (Quintile 2), 77 to ≤90 mg/dL (Quintile 3), 90 to ≤106 mg/dL (Quintile 4), and ≥106 mg/dL (Quintile 5)	Primary: Patients in the lowest LDL-C Quintiles were associated with the most reduction in the primary endpoint (P<0.0001). Secondary: Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of death from CHD (P<0.01). Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of nonfatal MIs (P<0.0001). Patients in the lowest LDL-C Quintiles were associated with the most reduction in the risk of stroke (P<0.05). There were no differences in the incidence of all-cause mortality across LDL-C Quintiles (P=0.104). There were no differences in the incidence of cardiovascular mortality across quintiles (P=0.060). There were no differences in the incidence of all-cause mortality across LDL-C Quintiles (P=0.653). There were no differences in the incidence of treatment-related adverse effects

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			Secondary: Any occurrence of a major coronary event, cerebrovascular event, hospitalization for heart failure, PAD, all-cause mortality, any cardiovascular event, and any coronary event among patients classified as Quintile 1, 2, 3, 4 or 5 (from above)	across LDL-C Quintiles (P value not reported).
Barter et al.[167] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease), stratified by HDL-C level	N=9,770 5 years	Primary: First major cardiovascular event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, fatal or nonfatal stroke) among patients with HDL-C <38 mg/dL (Quintile 1), 38 to 42 mg/dL (Quintile 2), 43 to 47 mg/dL (Quintile 3), 48	Primary: Patients in the highest HDL-C Quintiles were associated with the greatest reduction in the primary endpoint (P=0.04). Compared to patients in HDL-C Quintile 1, patients classified as HDL-C Quintile 5 had a 25% reduction in risk of a major cardiovascular event (HR, 0.75; 95% CI, 0.60 to 0.95). An increase in 1 mg/dL in HDL-C reduces the risk of major cardiovascular events by 1.1% at three months (P=0.003). Patients with the lowest LDL-C:HDL-C were at a significantly lower risk for major cardiovascular events (P=0.006). Patients with the lowest TC:HDL-C were at a significantly lower risk for major cardiovascular events (P value not reported). Among patients whose LDL-C was <70 mg/dL, those in the highest HDL-C

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			to 54 mg/dL (Quintile 4), and ≥55 mg/dL (Quintile 5) Secondary: Not reported	Quintile were at the lowest risk for a major cardiovascular event (P=0.03). Secondary: Not reported
Shepherd et al.[168] (2007) TNT Atorvastatin 10 mg/day vs atorvastatin 80 mg/day	Post hoc analysis of TNT Patients 35 to 75 years of age with CHD (either previous MI, coronary revascularization, angina with objective evidence of coronary disease)	N=9,770 5 years	Primary: GFR Secondary: Not reported	Primary: Eighty mg was associated with a significant increase in GFR from baseline over the five-year trial period compared to 10 mg (P<0.0001). Secondary: Not reported
Pitt et al.[169] (1999) AVERT Atorvastatin 80 mg/day vs percutaneous coronary transluminal angioplasty	MC, OL, RCT Adult patients with stable CAD, LDL-C ≥115 mg/dL, TG ≤500 mg/dL, stenosis ≥50% in ≥1 coronary artery and had been recommended for treatment with percutaneous revascularization, asymptomatic or with Canadian Cardiovascular	N=341 18 months	Primary: Number of ischemic events and/or need for re-vascularization, angina symptoms, adverse events Secondary: Not reported	Primary: Atorvastatin was associated with a significantly lower incidence of ischemic events compared to revascularization procedure (21 vs 13%; P=0.048). Atorvastatin was associated with a significantly longer time to the first ischemic event compared to revascularization procedure (P=0.03). A significantly smaller proportion of patients receiving atorvastatin had an improvement in the Canadian Cardiovascular Society classification of angina symptoms compared to revascularization procedure (41 vs 54%; P=0.009). Adverse events were similar between the two treatments (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	Society Class I or II angina, able to complete ≥4 minutes of a treadmill test or a bicycle exercise test without marked ECG changes indicative of ischemia			
Athyros et al.[170] (2002) GREACE Atorvastatin 10 mg/day, titrated up to 80 mg/day vs usual medical care (lifestyle modification and pharmacotherapy, including lipid lowering agents)	RCT Adult patients with established CHD not at LDL-C goal (<100 mg/dL) according to the NCEP criteria	N=1,600 3 years	Primary: Death, nonfatal MI, unstable angina, CHF, revascularization (coronary morbidity), stroke Secondary: Safety	Primary: Compared to usual care, atorvastatin was associated with a significant 51% reduction in the risk for CHD recurrent events or death (24.5 vs 12.0%; P<0.0001). Compared to usual care, atorvastatin was associated with a significant 43% reduction in all-cause mortality (5.0 vs 2.9%; P=0.0021). Compared to usual care, atorvastatin was associated with a significant 47% reduction in the risk of stroke (2.1 vs 1.1%; P=0.034). Compared to usual care, atorvastatin was associated with a significant 47% reduction in the risk of coronary mortality (4.8 vs 2.5%; P=0.0017). Compared to usual care, atorvastatin was associated with a significant 54% reduction in the risk of coronary morbidity (P<0.0001). Atorvastatin was associated with a reduction in TC by 36%, LDL-C by 46%, TG by 31% and non-HDL-C by 44% and an increase in HDL-C by seven percent (P value not reported). Compared to usual care, a greater proportion of patients receiving atorvastatin achieved the NCEP LDL-C goals (3 vs 95%, respectively; P value not reported). Compared to usual care, a greater proportion of patients receiving atorvastatin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				achieved the NCEP non-HDL-C goals (14 vs 97%, respectively; P value not reported). Secondary: Withdrawals due to adverse effects were similar between the two treatments (0.75 vs 0.40%; P value not reported).
Athyros et al[171] (2007) GREACE Atorvastatin 10 mg/day, titrated up to 80 mg/day vs usual medical care (lifestyle modification and pharmacotherapy, including lipid lowering agents)	Post hoc analysis of GREACE Adult patients with established CHD not at LDL-C goal (<100 mg/dL) according to the NCEP criteria, stratified by the presence of metabolic syndrome	N=1,600 3 years	Primary: Vascular events, estimated GFR, serum uric acid level Secondary: Not reported	Primary: Among patients with metabolic syndrome, atorvastatin was associated with a significant 57% reduction in the incidence of vascular events compared to usual medical care (12.1 vs 28.0%; RR, 0.43; 95% CI, 0.20 to 0.64; P<0.0001). Among patients without metabolic syndrome, atorvastatin was associated with a significant 41% reduction in the incidence of vascular events compared to usual medical care (RR, 0.59; 95% CI, 0.41 to 0.79; P<0.0001). Atorvastatin was associated with a significant increase in GFR and a reduction in serum uric acid level from baseline (P<0.05), regardless of metabolic syndrome status. Usual medical care was associated with a significant reduction in GFR and an increase in serum uric acid level from baseline (P<0.05), regardless of metabolic syndrome status. Compared to patients without metabolic syndrome, patients with metabolic syndrome experienced a greater increase in GFR with atorvastatin (P=0.02). Secondary: Not reported
Schwartz et al.[172] (2005) MIRACL Atorvastatin 80 mg/day vs placebo Treatment was	DB, MC, RCT Patients >18 years of age with unstable angina or non-Q-wave acute MI, with chest pain or discomfort ≥15 minutes that occurred at rest or with minimal exertion within	N=3,086 16 weeks	Primary: A composite endpoint of death, nonfatal acute MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischemia with objective	Primary: Compared to placebo, atorvastatin was associated with a 16% reduction in the risk of a composite endpoint of death, nonfatal acute MI, resuscitated cardiac arrest and recurrent symptomatic myocardial ischemia requiring hospitalization (17.4 vs 14.8%; P=0.048). Secondary: Compared to placebo, atorvastatin was associated with a significant 26% reduction in the risk of a recurrent ischemia requiring hospitalization (RR, 0.74; 95% CI, 0.57 to 0.95; P=0.02). Compared to placebo, atorvastatin was associated with a significant 50%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
administered within 96 hours of hospital admission with an ACS.	the 24 hour period preceding hospitalization and representing a change from their usual anginal pattern		evidence requiring hospitalization Secondary: Occurrence of the individual components of the primary endpoint, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospitalization but without new objective evidence of ischemia and coronary revascu-larization; time to occurrence of any of the above; percent changes from baseline in lipid levels; safety	reduction in the risk of a fatal and nonfatal stroke (RR, 0.50; 95% CI, 0.26 to 0.99; P=0.045). There were no significant differences between the two treatments in the incidence of coronary revascularization procedures, worsening heart failure, worsening angina, occurrence of at least one secondary endpoint or occurrence of at least one primary or secondary endpoint (P value not reported). Liver transaminase elevation was more common with atorvastatin (2.5 vs 0.6%; P<0.001).
Olsson et al.[173] (2007) MIRACL	Post hoc analysis of MIRACL Patients ≥65 years	N=3,086 16 weeks	Primary: A composite endpoint of death, nonfatal	Primary: Compared to placebo, atorvastatin was associated with a nonsignificant 14% reduction in the RR of the primary endpoint in patients ≥65 years of age (HR, 0.86; 95% CI, 0.70 to 1.07; ARR, 2.9%; P=0.18).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 80 mg/day vs placebo Treatment was administered within 96 hours of hospital admission with an ACS.	of age with unstable angina or non-Q-wave acute MI, with chest pain or discomfort ≥15 minutes duration that occurred at rest or with minimal exertion within the 24 hour period preceding hospitalization and representing a change from their usual anginal pattern		acute MI, resuscitated cardiac arrest or recurrent symptomatic myocardial ischemia with objective evidence requiring hospitalization among patients ≥65 and <65 years of age Secondary: Occurrence of the individual components of the primary endpoint, nonfatal stroke, new or worsening heart failure requiring hospitalization, worsening angina requiring hospitalization but without new objective evidence of ischemia, coronary revascu-	Compared to placebo, atorvastatin was associated with a nonsignificant 22% reduction in the RR of the primary endpoint in patients <65 years of age (HR, 0.78; 95% CI, 0.56 to 1.06; ARR, 2.5%; P=0.11). Secondary: There was no significant difference in any of the secondary endpoints between patients ≥65 and <65 years of age (P>0.05). The frequency of adverse events was similar between the two treatments (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			larization, time to occurrence of any of the above; percent change from baseline in lipid levels among patients ≥65 and <65 years of age; safety	
Amarenco et al.[174] (2006) SPARCL Atorvastatin 80 mg/day vs placebo	DB, PC, RCT Patients ≥18 years of age who had an ischemic or hemorrhagic stroke or TIA 1 to 6 months before trial entry (patients with a prior hemorrhagic stroke could be included if they were deemed to be at risk for ischemic stroke or CHD) and LDL-C ≥100 to ≤190 mg/dL	N=4,731 4.9 years	Primary: Time to first occurrence of a nonfatal or fatal stroke Secondary: Occurrence of major cardiovascular events (stroke, cardiac death, nonfatal MI or resuscitated cardiac arrest)	Primary: Patients with a reduction in LDL-C >16% had a significant reduction in stroke compared to those with a reduction <16% (11.0 vs 13.4%; HR, 0.792; 95% CI, 0.671 to 0.935; P=0.0058). Secondary: Patients with a reduction in LDL-C >16% had a significant reduction in major cardiovascular events compared to those with a reduction <16% (13.9 vs 17.3; HR, 0.761; 95% CI, 0.657 to 0.881; P=0.0003).
Amerenco et al[175] Atorvastatin 80 mg/day vs placebo	Subanalysis of SPARCL to evaluate stroke subtypes Patients ≥18 years of age who had an ischemic or	N=4,731 4.9 years	Primary: Time to first occurrence of a nonfatal or fatal stroke Secondary: Occurrence of	Primary: Atorvastatin was similarly effective in reducing the primary endpoint for all entry event stroke subtypes (large vessel, TIA, small vessel and unknown). Although there was no overall heterogeneity between subtypes, the patients with baseline hemorrhagic stroke receiving atorvastatin were qualitatively different and were more than three times more likely to have a recurrent stroke compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	hemorrhagic stroke or TIA 1 to 6 months before trial entry (patients with a prior hemorrhagic stroke could be included if they were deemed to be at risk for ischemic stroke or CHD) and LDL-C ≥100 to ≤190 mg/dL		major cardiovascular events (stroke, cardiac death, nonfatal MI or resuscitated cardiac arrest), all-cause mortality	Secondary: Atorvastatin was similarly effective in reducing the occurrence of major cardiovascular events for all entry event stroke subtypes (large vessel, TIA, small vessel and unknown). Mortality rates were similar across all entry event stroke subtypes. The analyses were also carried out with adjustment for BP, diabetes and ambulatory score at baseline and the results did not differ.
Sang et al.[176] (2009) Atorvastatin 10 mg/day vs atorvastatin 10 mg/day and niacin ER	RCT Patients with clinical and angiographic criteria for coronary disease, with ≥50% stenosis of 1 coronary artery with high TC	N=108 12 months (plus a 12 month follow up)	Primary: All-cause mortality, MI, rehospitalization, revascularization with either PCI or CABG Secondary: Mean percent changes from baseline lipid parameters, effects on glucose metabolism, safety	Primary: At 12 months, clinical events included rehospitalization due to angina pectoris and heart failure attack, respectively, revascularization with PCI and sudden death (7.14%) with atorvastatin. With combination therapy, the clinical events included rehospitalization due to heart failure attack, revascularization after PCI or CABG (5.77%). No significant reduction was observed with combination therapy (OR, 0.78; P=0.052). Secondary: TC, TG, LDL-C and Lp(a) levels decreased significantly with both treatments (P<0.01), with no significant difference between the two during the course of follow up (P>0.05). Apo A increased significantly with both treatments (P<0.01), with a more favorable effect observed with combination therapy (24.5 vs 40.8%; P<0.01). During the follow up, apo B fell by 5.63 (P<0.05 and 7.35% (P<0.01) with atorvastatin and combination therapy; with no significant difference between the two (P>0.05). During the trial, HDL-C levels increased by 11.67 (P<0.05) and 29.36% (P<0.01) with atorvastatin and combination therapy, with a significant difference favoring combination therapy (P<0.01). Niacin resulted in no significant increase in glucose levels at six or 12 months compared to baseline levels (P>0.05). In the subgroup of diabetic patients (n=28), niacin resulted in a significant increase in glucose levels at six months (P<0.01), and glucose levels increased more significantly at 12 months

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				(P<0.01), but the effect of niacin was not significant in nondiabetic patients (P>0.05). HbA_{1c} levels did not show a significant increase at six months in patient with diabetes, but levels increased significantly at 12 months (P<0.05). Both treatments were generally well tolerated. The most common side effect of niacin therapy was flushing which appeared in four patients receiving combination therapy; however, all patients continued the medication and the flushing disappeared.
Serruys et al.[177] (2002) LIPS Fluvastatin 40 mg BID vs placebo	DB, MC, PC, RCT Patients 18 to 80 years of age with angina or silent ischemia following successful completion of their first PCI, with baseline TC 135 to 270 mg/dL and fasting TG <400 mg/dL	N=1,677 3 to 4 years	Primary: Incidence of major adverse cardiac events (cardiac death, nonfatal MI or a reintervention procedure of CABG or repeat PCI) Secondary: Major adverse cardiac events excluding reintervention procedures (surgical or PCI) occurring in the first six months of follow up for lesions treated at the index procedure, cardiac mortality, combined cardiac	Primary: Major adverse cardiac event-free survival time was significantly longer with fluvastatin compared to placebo (P=0.01). Major adverse cardiac events occurred significantly less frequently with fluvastatin compared to placebo (21.4 vs 26.7%; RR, 0.78; 95% CI, 0.64 to 0.95; P=0.01). During the follow up period, 13 patients (1.5%) receiving fluvastatin compared to 24 patients (2.9%) receiving placebo died from cardiac causes, 30 patients (3.6%) compared to 38 patients (4.6%) had a nonfatal MI and 167patients (19.8%) compared to193 patients (23.2%) underwent CABG or PCI (P values not reported). Secondary: The risk of major adverse cardiac events, excluding reintervention procedures (surgical or PCI), occurring in the first six months of follow up for lesions treated at the index procedure was 33% lower (RR, 0.67; 95% CI, 0.54 to 0.8; P<0.001) with fluvastatin. There was no difference in the reduction of cardiac mortality, combined cardiac mortality and MI and combined all-cause mortality and MI between the two treatments (P=0.07, P=0.07 and P=0.08, respectively). After six weeks, fluvastatin significantly reduced LDL-C by 27% (95% CI, 25 to 29% compared to an 11% reduction with placebo (95% CI, 9 to 13; P<0.001). TG reductions were greater with fluvastatin compared to placebo (22 vs 14%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			mortality and MI, combined all-cause mortality and MI, treatment effects on measured lipid levels, discontinuation rates, tolerability, safety	P value not reported). HDL-C increased by a median of 22% with both treatments (P value not reported). Discontinuation rates due to adverse events were 21.2 and 24.0% with fluvastatin and placebo. Death rates due to noncardiac causes were 2.7 and 3.0% with fluvastatin and placebo. There were three reported cases of elevations in CK ≥10 times the upper limit of normal with placebo. There were 10 patients receiving fluvastatin and three patients receiving placebo who had elevations of at least three times the upper limit of normal level in AST or ALT on two consecutive occasions. Cancers were reported in 46 and 49 patients receiving fluvastatin and placebo (P values not reported).
Liem et al.[178] (2002) FLORIDA Fluvastatin 80 mg/day vs placebo	DB, PC, PG, RCT Adult patients with an acute MI and TC <6.5 mmol/L, new or markedly increased chest pain lasting >30 minutes or a new pathological Q wave ≥0.04 seconds duration, or ≥25% of the corresponding R wave amplitude, both in ≥2 contiguous leads	N=540 1 year	Primary: Presence of either ischemia on ambulatory ECG monitoring at 12 months or the occurrence of a major clinical event Secondary: Six week and 12 month incidence of ischemia on the ambulatory ECG, six week and 12 month change in ischemic burden, 12 month change in lipid profile,	Primary: After 12 months, fluvastatin did not significantly affect ischemia on ambulatory ECG (P=0.67), nor the occurrence of any major clinical event (P=0.24) when compared to placebo. Secondary: In patients with ischemia at baseline, 29 and 38% receiving fluvastatin and placebo were ischemic on the ambulatory ECG at six weeks and 27 and 21% were again positive for ischemia at 12 months (P value not reported). The six week and 12 month ischemic burden was lowered by 6.1 and 7.7%, respectively, with fluvastatin and by 10.5 and 13.0%, respectively, with placebo (P=0.81 and P=0.43, respectively between treatment groups). After 12 months, fluvastatin lowered LDL-C by 21% compared to an increase of nine percent with placebo (P<0.001). There were 62 and 68 patients receiving fluvastatin and placebo who had at least one major clinical event (P=0.764). All-cause mortality was 2.6 and 4.0% with fluvastatin and placebo (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			safety and tolerability	
Sacks et al.[179] (1996) CARE Pravastatin 40 mg QD vs placebo	DB, MC, RCT Adult post MI patients with TC <240 mg/dL, LDL-C 115 to 174 mg/dL, TG <350 mg/dL, glucose ≤220 mg/dL, left ventricular ejection fractions ≥25 percent and no symptomatic CHF	N=4,159 5 years	Primary: Death from CHD (including fatal MI, either definite or probable, sudden death, death during a coronary intervention and death from other coronary causes) or a symptomatic nonfatal MI confirmed by serum CK Secondary: Not reported	Primary: When compared to placebo, there was a significant 24% lower incidence of the primary endpoint with pravastatin (13.2 vs 10.2%; 95% CI, 9 to 36; P=0.003). Pravastatin was associated with a significant 23% risk reduction in nonfatal MIs compared to placebo (P=0.02). Pravastatin was associated with a nonsignificant 37% reduction in the rate of fatal MIs (95% CI, -5 to 62; P=0.07) and a nonsignificant 25% reduction in the rate of total MIs (95% CI, 8 to 39; P=0.06) compared to placebo. Secondary: Not reported
No authors listed.[180] (1998) LIPID Pravastatin 40 mg QD vs placebo	DB, MC, PC Patients 31 to 75 years of age who were post MI or who had a hospital discharge diagnosis of unstable angina between 3 and 36 months before trial entry	N=9,014 6.1 years	Primary: Death from CHD Secondary: Incidence of MI and stroke, rate of CABG surgery	Primary: Death from CHD occurred in 6.4 and 8.3% of patients receiving pravastatin and placebo (RRR, 24%; 95% CI, 12 to 35; P<0.001). Secondary: Pravastatin was associated with a significant 29% reduction in the incidence of MI compared to placebo (7.4 vs 10.3%; P<0.001). Pravastatin was associated with a significant 19% reduction in the incidence of stroke compared to placebo (3.7 vs 4.5%; P=0.048). Pravastatin was associated with a significant 22% reduction in the risk of CABG surgery compared to placebo (9.2 vs 11.6%; P<0.001). Pravastatin was associated with a significant 19% reduction in the risk of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				coronary angioplasty compared to placebo (4.7 vs 5.6%; P=0.024). Pravastatin was associated with a significant 12% reduction in the risk of unstable angina compared to placebo (22.3 vs 24.6%; P=0.005).
Shepherd et al.[181] (2002) PROSPER Pravastatin 40 mg QD vs placebo	DB, MC, PC, RCT Patients 70 to 82 years of age with pre-existing vascular disease (coronary, cerebral or peripheral) or at an increased risk of such disease due to risk factors (smoking, HTN, or diabetes) with TC 4 to 9 mmol/L and TG <6 mmol/L	N=5,804 Mean, 3.2 years (range, 2.8 to 4.0 years)	Primary: Combined endpoint of definite or suspect death from CHD, nonfatal MI and fatal or nonfatal stroke Secondary: Examination of coronary and cerebrovascular components separately, assessment of cognitive function, adverse events, cancer	Primary: Pravastatin was associated with a significant 15% reduction in the risk of the primary endpoint compared to placebo (14.1 vs 16.2%; HR, 0.85; 95% CI, 0.74 to 0.97; P=0.014). Secondary: When the primary endpoint was separated into coronary and cerebrovascular components, the authors noted a 19% reduction in coronary events with pravastatin, but no apparent effect on cerebrovascular events (P value not reported). Pravastatin was associated with a significant 19% reduction in the risk of CHD death or nonfatal MI compared to placebo (10.1 vs 12.2%; HR, 0.81; 95% CI, 0.69 to 0.94; P=0.006). When examining the rates of fatal or nonfatal stroke, there was no significant difference between the two treatments (HR, 1.03; 95% CI, 0.81 to 1.31; P=0.81). There was no significant difference in cognitive function between the two treatments (P>0.05). The rate of serious adverse events reported was similar between the two treatments (56 vs 55%, respectively; P value not reported). There were no patients with either treatment reported rhabdomyolysis or CK concentrations >10 times the upper limit of normal (P value not reported). There were no significant differences in the rates of cancer development between the two treatments (P>0.05).
Thompson et al.[182] (2004) PACT	DB, MC, PC, RCT Patients 18 to 85	N=3,408 4 weeks	Primary: Composite of death from any cause, acute MI	Primary: Pravastatin 40 mg was associated with a nonsignificant 6.4% reduction in the risk of the primary endpoint compared to placebo (P=0.48).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Pravastatin 20 to 40 mg/day vs placebo	years of age with <24 hours onset of symptoms and diagnosis of acute MI or unstable angina pectoris		or readmission to hospital with unstable angina pectoris during the first month following randomization Secondary: Incidence of individual causes of death, acute MI other than the index event, readmission for angina in the first month, urgent revascularization procedure, other nonfatal cardiovascular events; adverse events	Secondary: There were no significant differences in the frequency of individual components of the primary endpoint in the 30 days after randomization between the two treatments (P>0.05). The frequency of adverse events did not differ between the two treatments (P value not reported).
Asselbergs et al.[183] (2004) Pravastatin 40 mg QD and fosinopril 20 mg QD vs placebo	DB, PC, RCT Patients aged 28-75 years with persistent micro-albuminuria, BP <160/100 mm Hg (not on antihypertensive medications), TC level <8.0 mmol/L, or <5.0	N=864 46 months	Primary: Combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity (nonfatal or myocardial ischemia, heart	Primary: Pravastatin therapy was associated with a 13% reduction in the risk of the primary end point compared to placebo (4.8 vs 5.6%; P=0.649). The incidence of non-cardiovascular mortality was 2.1% in the pravastatin group compared to 1.9% in the placebo group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	mmol/L in case of previous MI, and no use of lipid-lowering medication		failure, peripheral vascular disease and/or cerebrovascular accident) Secondary: Not reported	
Sato et al.[184] (2008) OACIS-LIPID Pravastatin 10 mg QD vs no pravastatin	MC, OL, RCT Patients with acute MI and mild to moderate hyperlipidemia (TC 200 to 250 mg/dL and TG ≤300 mg/dL)	N=353 9 months	Primary: Composite end point of death, nonfatal MI, unstable angina, re-vascularization and non-fatal stroke, and rehospitalization because of other cardiovascular diseases Secondary: Not reported	Primary: The composite end point occurred in 17.9% of patients in the pravastatin group compared to 31.4% of patients in the non-pravastatin group (HR, 0.56; 95% CI, 0.36 to 0.87; P<0.006). There were no significant differences in the risk of death (P=0.643), nonfatal MI (P=0.622), unstable angina (P=0.985), or nonfatal stroke (P=0.252) between the pravastatin group and non-pravastatin group. There was a lower risk of revascularization in the pravastatin group compared to the non-pravastatin group (12.7 vs 20.6%, P=0.049). Secondary: Not reported
Tavazzi et al.[185] (2008) GISSI-HF Rosuvastatin 10 mg QD vs placebo	RCT, DB, MC, PC Patients ≥18 years of age with symptomatic heart failure (NYHA class II to IV)	N=4,631 Median 3.9 years	Primary: Time to death, and time to death or admission to hospital for cardiovascular reasons Secondary: Cardiovascular	Primary: At the end of the follow-up period, 29% of patients in the rosuvastatin group died from any cause compared to 28% of patients in the placebo group (HR, 1.00; 97% CI, 0.898 to 1.122; P=0.943). The composite of all-cause death or admission to hospital for cardiovascular reasons occurred in 57% of patients in the rosuvastatin group compared to 56% of patients in the placebo group (HR, 1.01; 99% CI, 0.908 to 1.112; P=0.903). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			mortality, cardiovascular mortality or admission for any reason, sudden cardiac death, admission for any reason, admission for cardiovascular reasons, admission for heart failure, MI, and stroke	There was no difference in cardiovascular mortality (P=0.804), first hospital admission for any, cardiovascular, or heart failure cause (P=0.962, P=0.613, and P=0.987, respectively), or the combined outcome measure of cardiovascular death or admission to hospital for any cause (P=0.409) sudden cardiac death (P=0.221), MI (P=0.459), and stroke (P=0.174) with rosuvastatin compared to placebo.
Rossebø et al.[186] (2008) SEAS Simvastatin 40 mg QD and ezetimibe 10 mg QD vs placebo Open-label lipid-lowering therapy, which included up to 40 mg of simvastatin or an equipotent dose of another lipid-lowering	DB, MC, RCT Patients 45 to 85 years of age who had asymptomatic, mild-to-moderate aortic valve stenosis with a peak aortic-jet velocity of 2.5 to 4 m per second	N=1,873 52.2 months (median duration)	Primary: Composite of major cardiovascular events (death from cardiovascular causes, aortic-valve replacement, CHF as a result of progression of aortic-valve stenosis, nonfatal MI, hospitalization for unstable angina, CABG, PCI, non-hemorrhagic	Primary: The composite of major cardiovascular events occurred in 35.3% of patients in the simvastatin plus ezetimibe group and in 38.2% of patients in the placebo group (HR, 0.96; 95% CI, 0.83 to 1.12; P=0.59). Secondary: There was no significant difference between the treatments in aortic-valve-related events (HR, 0.97; 95% CI, 0.83 to 1.14; P=0.73). Aortic-valve replacement occurred in 28.3% of patients in the simvastatin plus ezetimibe group and in 29.9% of patients in the placebo group (HR, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Ischemic cardiovascular events occurred in 15.7% of patients in the simvastatin plus ezetimibe group compared to 20.1% of patients in the placebo group (HR, 0.78; 95% CI, 0.63 to 0.97; P=0.02). A total of 7.3% of patients in the simvastatin plus ezetimibe group required CABG compared to 10.8% of patients in the placebo group (HR, 0.68; 95% CI, 0.50 to 0.93; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
drug, could be administered in addition to the study drug at the discretion of each treating physician			stroke) Secondary: Aortic-valve events, progression of aortic stenosis, safety	There was no significant difference in the progression of aortic stenosis between the treatment groups. The mean peak aortic jet velocity was 3.71 m per second in the placebo group compared to 3.69 m per second in the simvastatin plus ezetimibe group at the end of the study (95% CI, -0.06 to 0.05; P=0.83). The mean pressure gradient increased to 34.4 mm Hg in the placebo group compared to 34.0±15.1 mm Hg in the simvastatin plus ezetimibe group at the end of the study. There was no significant difference in the aortic-valve area between the treatment groups. There was no significant difference in overall mortality among the treatment groups (P=0.80). The composite outcome of death from cardiovascular causes and the individual components of this composite outcome did not differ significantly between the two groups (P=0.34). There was a significant increase in the number of patients with elevated liver enzyme levels in the simvastatin plus ezetimibe group. There was also a higher incidence of cancer in the simvastatin plus ezetimibe group (11.1%) compared to placebo (7.5%; P=0.01).
No authors listed.[187] (1994) 4S Simvastatin 10 mg/day, titrated up to 40 mg/day vs placebo	DB, PC, RCT Patients 35 to 70 years of age with CHD, a history of angina pectoris or previous MI, TC 212 to 309 mg/dL and TG <221 mg/dL on a lipid-lowering diet	N=4,444 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal acute MI, resuscitated cardiac arrest and definite silent MI)	Primary: Simvastatin was associated with a 30% reduction in all-cause mortality compared to placebo (8 vs 12%; RR, 0.70; 95% CI, 0.58 to 0.85; P=0.0003). Secondary: Overall, patients receiving placebo experienced at least one secondary event compared to patients receiving simvastatin (28 vs 19%, respectively; P value not reported). There were 189 (8.5%) coronary deaths with placebo compared to 111 (5.0%) coronary deaths with simvastatin (RR, 0.58; 95% CI, 0.46 to 0.73; P value not reported). There were 270 (12.1%) definite acute MI with placebo compared to 164 (7.4%) definite acute MI with simvastatin. There were 418 (18.8%) definite or probable acute MI with placebo compared to 279 (12.6%) definite or probable acute MI with simvastatin. There were 110 (4.9%) silent MIs with placebo compared to 88 (4.0%) silent MIs with simvastatin. There was one patient receiving simvastatin who experienced resuscitated cardiac arrest. (P

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				values not reported). Additionally, a cerebrovascular event occurred in 95 (4.3%) patients with placebo compared to 61 (2.7%) patients with simvastatin (RR, 95% CI; P value not reported).
Chonchol et al.[188] 4S (2007) Simvastatin 10 mg/day, titrated up to 40 mg/day vs placebo	Subanalysis of 4S Patients 35 to 70 years of age with CHD, a history of angina pectoris or previous MI, TC 212 to 309 mg/dL and TG <221 mg/dL on a lipid-lowering diet, stratified by estimated GFR of ≥75 or <75 mL/min/1.73 m^2	N=4,420 5.4 years	Primary: All-cause mortality Secondary: Major coronary events (coronary deaths, definite or probable hospital-verified nonfatal acute MI, resuscitated cardiac arrest and definite silent MI)	Primary: Simvastatin was associated with a significant reduction in all-cause mortality among patients with chronic renal insufficiency (HR, 0.70; 95% CI, 0.55 to 0.91; P value not reported). Secondary: Simvastatin was associated with a significant reduction in the incidence of major coronary events among patients with chronic renal insufficiency (HR, 0.68; 95% CI, 0.57 to 0.80; P value not reported). Simvastatin was associated with a significant reduction in the incidence of CHD deaths or nonfatal MIs among patients with chronic renal insufficiency (HR, 0.66; 95% CI, 0.55 to 0.79; P value not reported). Simvastatin was associated with a significant reduction in the incidence of coronary revascularization among patients with chronic renal insufficiency (HR, 0.63; 95% CI, 0.51 to 0.79; P value not reported). Simvastatin was not associated with a significant reduction in the incidence of stroke among patients with chronic renal insufficiency (HR, 0.86; 95% CI, 0.54 to 1.36; P value not reported).
No authors listed.[189] (2003) MRC/BHF (HPS) Simvastatin 40 mg QD vs placebo	DB, MC, PC, RCT Patients 40 to 80 years of age with a history of CHD, PAD, cerebrovascular disease, diabetes or treated HTN (if also male and ≥65 years of age) with TC ≥135 mg/dL	N=20,536 5 years	Primary: All-cause mortality and CHD death events Secondary: Noncoronary causes of death, major coronary events (nonfatal MI or CHD death), stroke,	Primary: During the trial, 12.9 (1,328/10,269) vs 14.7% (1,507/10,267) of patients receiving simvastatin and placebo died (P=0.0003). The effect of simvastatin on all-cause mortality was mainly due to the definite 17% (SE, 4; 95% CI, 9 to 25) proportional reduction in the death rate from vascular causes (7.6 vs 9.1%; P<0.0001), which consists of a highly significant 18% (SE, 5) reduction in the coronary death rate (5.7 vs 6.9%; P=0.0005) and a nonsignificant 16% (SE, 9) reduction in the death rate from other vascular causes (1.9 vs 2.2%; P=0.07). There were no differences in all nonvascular deaths (5.3 vs 5.6%; P=0.4) or in any of the prespecified categories of nonvascular deaths (renal, hepatic and trauma). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			revascularization, major vascular events (nonfatal MI, CHD death, stroke or revascularization), cancer	Simvastatin was associated with a significant 38% (SE, 5; 95% CI, 30 to 46) proportional reduction in the incidence rate of first nonfatal MI (3.5 vs 5.6%; P<0.0001). For the endpoint of major coronary events, there was a significant 27% (SE, 4; 95% CI, 21 to 33) proportion reduction in the incidence rate of combined first nonfatal MI or coronary death (8.7 vs 11.8%; P<0.0001). Overall, simvastatin was associated with a significant 25% (SE, 5; 95% CI, 15 to 34) proportional reduction in the incidence rate of fist stroke (4.3 vs 5.7%; P<0.0001). This was due to mainly to a significant 30% (SE, 6; 95% CI, 19 to 40) proportional reduction in the incidence rate of strokes attributed to ischemia (2.8 vs 4.0%; P<0.0001), with no apparent difference in strokes attributed to hemorrhage (0.5 vs 0.5%; P=0.8). Overall, simvastatin was associated with a significant 24% (SE, 4; 95% CI, 17 to 30) proportional reduction in the incidence rate of first revascularization procedure (9.1 vs 11.7%; P<0.0001). Specifically, simvastatin was associated with a significant 30% (SE, 5; 95% CI, 22 to 38) proportional reduction in the incidence rate of coronary revascularization (5.0 vs 7.1%; P<0.0001). Similar results were observed for noncoronary revascularization (4.4 vs 5.2%; P=0.006). When the data for major coronary events (first nonfatal MI or coronary death), stroke and revascularization are combined for the endpoint of major vascular events, simvastatin was associated with a significant 24% (SE, 3; 95% CI, 19 to 28) proportional reduction in the event rate (19.8 vs 25.2%; P<0.001). New primary cancers were diagnosed in 7.9 and 7.9% of patients receiving simvastatin and placebo (rate ratio, 1.00; 95% CI, 0.91 to 1.11). These cases were associated with death in 3.5 vs 3.4% of patients (rate ratio, 1.03; 95% CI, 0.89 to 1.19). There were also no differences in the incidence of cancers in any particular body system.
Collins et al.[190] (2007) MRC/BHF (HPS) Simvastatin 40 mg QD	DB, MC, PC, RCT Patients 40 to 80 years of age with a history of CHD,	N=20,536 (5,963 diabetics and 14,573 patients with occlusive arterial disease without diabetes)	Primary: Incidence of first nonfatal MI or coronary death; fatal or nonfatal stroke;	Primary: Simvastatin was associated with a significant 27% reduction in the incidence of first nonfatal MI or coronary death compared to placebo (95% CI, 21 to 33; P<0.0001). Among diabetic patients, simvastatin was associated with a significant 27%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo	PAD, cerebrovascular disease, diabetes or treated HTN (if also male and ≥65 years of age) with TC ≥135 mg/dL	5 years	revascular-ization procedures; first incidence of major coronary events, strokes and revascular-izations Secondary: Not reported	reduction in the incidence of first nonfatal MI or coronary death compared to placebo (95% CI, 19 to 34; P<0.0001). Simvastatin was associated with a significant 25% reduction in the incidence of first nonfatal or fatal strokes compared to placebo (95% CI, 15 to 34; P<0.0001). Simvastatin was associated with a significant 26% reduction in the incidence of fatal strokes compared to placebo (95% CI, 14 to 36; P=0.0002). Among diabetic patients, simvastatin was associated with a significant 24% reduction in the incidence of fatal strokes compared to placebo (95% CI, 6 to 39; P=0.01). Simvastatin was associated with a significant 24% proportional reduction in the incidence of first revascularization compared to placebo (95% CI, 17 to 30; P<0.0001). Among diabetic patients, simvastatin was associated with a significant 17% reduction in the incidence of first revascularization procedure compared to placebo (95% CI, 3 to 30; P=0.02). Simvastatin was associated with a significant 24% reduction in the first incidence of major coronary events, strokes and revascularizations compared to placebo (95% CI, 19 to 28; P<0.0001). Among diabetic patients, simvastatin was associated with a significant 22% reduction in the incidence of first incidence of major coronary events, strokes and revascularizations compared to placebo (95% CI, 13 to 30; P<0.0001). Secondary: Not reported
de Lemos et al.[191] (2004) A to Z trial Simvastatin 40	DB, MC, PC Adult patients with either non-ST-elevation ACS	N=4,497 2 years	Primary: Composite of cardiovascular death, nonfatal MI,	Primary: Simvastatin 80 mg was associated with a nonsignificant reduction in the risk of the primary endpoint compared to simvastatin 20 mg (14.4 vs 16.7%; HR, 0.89; 95% CI, 0.76 to 1.04; P=0.14).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
mg/day for 1 month, titrated up to 80 mg/day (intensive therapy) vs placebo for 4 months, followed by simvastatin 20 mg/day (delayed initiation of a less intensive therapy)	or STEMI		readmission for ACS (requiring new ECG changes or cardiac marker elevation) and stroke Secondary: Individual components of the primary endpoint, re-vascularization due to documented ischemia, all-cause mortality, new-onset CHF (requiring admission or initiation of heart failure medications), cardiovascular Re-hospitalization	Secondary: Simvastatin 80 mg was associated with a significant reduction in the risk of cardiovascular death compared to simvastatin 20 mg (HR, 0.75; 95% CI, 0.57 to 1.00; P=0.05). There was no significant difference between the two treatments in the secondary endpoints of MI, readmission for ACS, revascularization due to documented ischemia or stroke (P>0.05 for all). Simvastatin 80 mg was associated with a significant reduction in the risk of new onset CHF compared to simvastatin 20 mg (3.7 vs 5.0%; HR, 0.72; 95% CI, 0.53 to 0.98; P=0.04).
No authors listed.[192] (2007) Simvastatin 40 mg QD vs placebo	DB, MC, RCT Patients 40 to 80 years of age with a history of CHD, PAD, cerebrovascular disease, diabetes or treated HTN (if also male and ≥65	N=20,536 5 years	Primary: The first major coronary event (nonfatal MI or coronary death), first major vascular event (major coronary event, stroke or	Primary: In the overall population, simvastatin was associated with a significant 24% reduction in the first incidence of a major vascular event compared to placebo (19.8 vs 25.2%; P<0.0001). Among patients with baseline PAD, simvastatin was associated with a significant 22% reduction in the first incidence of a major vascular event compared to placebo (26.4 vs 32.7%; P<0.0001). Among patients without baseline PAD, simvastatin was associated with a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	years of age) with TC ≥135 mg/dL		revascular-ization) Secondary: Not reported	significant 25% reduction in the first occurrence of a major vascular event compared to placebo (16.5 vs 21.5%; P<0.0001). The difference in the reduction of the risk of major vascular events with statin therapy between the PAD and non-PAD groups was not significant (P=0.05). In the overall population, simvastatin was associated with a significant 27% reduction in the first incidence of a major coronary event compared to placebo (8.7 vs 11.8%; P<0.0001). Among patients with baseline PAD, simvastatin was associated with a significant reduction in the first incidence a major coronary event compared to placebo (10.9 vs 13.8%; P<0.0001). Among patients without baseline PAD, simvastatin was associated with a significant reduction in the first incidence of a major coronary event compared to placebo (7.7 vs 10.8%; P<0.0001). The difference in the reduction of the risk of major coronary events with statin therapy between the PAD and non- PAD groups was not significant (P=0.03). In the overall population, simvastatin was associated with a significant 25% reduction in the first incidence of stroke compared to placebo (4.3 vs 5.7%; P<0.0001). Among patients with baseline PAD, simvastatin was associated with a significant reduction in the first incidence of stroke compared to placebo (5.3 vs 7.2%; P<0.0001). Among patients without baseline PAD, simvastatin was associated with a significant reduction in the first incidence of stroke compared to placebo (3.8 vs 5.0%; P<0.0001). The difference in the reduction of the risk of stroke with statin therapy between the PAD and non-PAD groups was not significant (P=0.07). In the overall population, simvastatin was associated with a significant 24% reduction in the first incidence of revascularization compared to placebo (9.1 vs 11.7%; P<0.0001). Among patients with baseline PAD, simvastatin was associated with a significant reduction in the first incidence of revascularization compared to placebo (13.8 vs 17.9%; P<0.0001). Among patients without baseline PAD, simvastatin was associated with a significant reduction in the first incidence of revascularization compared to placebo (6.9 vs 8.7%; P<0.0001). The difference in the reduction of the risk of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				revascularization with statin therapy between the PAD and non- PAD groups was not significant (P=0.07). In the overall population, simvastatin was associated with a significant 16% reduction in the risk of first incidence of a peripheral vascular event compared to placebo (4.7 vs 5.5%; P=0.006). This risk reduction was independent of baseline LDL-C, age, diabetes or coronary disease (P values not reported). Secondary: Not reported
Briel et al.[193] (2006) Statins (pravastatin 10 to 40 mg, fluvastatin 80 mg, atorvastatin 20 to 80 mg, simvastatin 40 to 80 mg) vs placebo	MA (12 PC, RCTs) Patients with ACS (MI or unstable angina), started on statin therapy within 14 days of ACS and with a follow up ≥30 days	N=13,024 ≥30 days	Primary: Composite endpoint of nonfatal MI, nonfatal stroke and total death Secondary: Total death, total MI, total stroke, cardiovascular death, fatal and nonfatal MI, revascularization procedures (CABG surgery, angioplasty) and unstable angina (recurrent myocardial ischemia requiring emergency hospitalization)	Primary: At either month one or four follow up, there was no significant difference in the primary endpoint between statin therapy and placebo (P=0.39 and P=0.30, respectively). Secondary: At either month one or four of follow up, there was no significant difference in any of the secondary endpoints (except for unstable angina) between statin therapy and placebo (P values not reported). After four months of therapy, statin therapy was associated with a significant moderate reduction in the incidence of unstable angina compared to placebo (P=0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Mood et al.[194] (2007) Statins (atorvastatin 20 to 40 mg/day, pravastatin 40 mg/day, fluvastatin 40 mg BID) vs placebo or usual care	MA (6 RCTs) Therapy was initiated around the time of a PCI	N=3,941 up to 45 months	Primary: Incidence of MI Secondary: All-cause mortality, cardiovascular mortality, surgical or percutaneous re-vascularization, stroke	Primary: Compared to placebo or usual care, statin therapy was associated with a significant 43% reduction in the risk for MI (5.2 vs 3.0%; OR, 0.57; 95% CI, 0.42 to 0.78; P<0.0001). Secondary: Compared to placebo or usual care, statin therapy was associated with a nonsignificant 26% reduction in all-cause mortality (3.0 vs 2.3%; OR, 0.74; 95% CI, 0.5 to 1.1; P=0.14). Compared to placebo or usual care, statin therapy was associated with a nonsignificant 42% reduction in cardiovascular mortality (1.20 vs 0.71%; OR, 0.58; 95% CI, 0.30 to 1.11; P=0.10). Compared to placebo or usual care, statin therapy was associated with a nonsignificant 11% reduction in the incidence of repeat surgical or percutaneous revascularization (21.9 vs 19.6%; OR, 0.89; 95% CI, 0.78 to 1.02; P=0.098). The incidence of stroke was nonsignificantly higher with statin therapy compared to placebo or usual care (0.40 vs 0.08%; OR, 3.00; 95% CI, 0.60 to 14.77; P=0.18).
Afilalo et al.[195] (2008) Moderate statin therapy (pravastatin 40 mg/day, fluvastatin 80 mg/day, simvastatin 20 to 40 mg/day) vs placebo	MA (9 RCTs) Patients ≥50 years of age with CHD	N=19,569 (9 studies) ≥6 months	Primary: All-cause mortality, CHD mortality, stroke, re-vascularization, nonfatal MI Secondary: Not reported	Primary: Statin therapy was associated with a lower rate of all-cause mortality compared to placebo (15.6 vs 18.7%; RR, 0.78; 95% CI, 0.65 to 0.89; P value not reported). Statin therapy was associated with a significant reduction in the risk of CHD mortality by 30% (RR, 0.70; 95% CI, 0.53 to 0.83), nonfatal MI by 26% (RR, 0.74; 95% CI, 0.60 to 0.89), revascularization by 30% (RR, 0.70; 95% CI, 0.53 to 0.83) and stroke by 25% (RR, 0.75; 95% CI, 0.56 to 0.94). The calculated NNT with statin therapy to save one life was 28 (95% CI, 15 to 56). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Hulten et al.[196] (2006) Intensive statin therapy (pravastatin 40 mg/day, fluvastatin 80 mg/day, simvastatin 80 mg/day, atorvastatin 20 mg/day, atorvastatin 80 mg daily) vs placebo or lower dosed statin therapy	MA (13 RCTs) Adult patients initiated on intensive statin therapy or control within 14 days of hospitalization for ACS	N=17,963 Up to 2 years of follow up	Primary: Composite of death, recurrent ischemia and recurrent MI; death and cardiovascular events; cardiovascular death; ischemia; MI; LDL-C reduction; safety Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with a significantly lower rate of mortality and cardiovascular events over 24 months of follow up (HR, 0.81; 95% CI, 0.77 to 0.87; P<0.001). In patients with recent ACS, intensive statin therapy was associated with a lower risk of overall cardiovascular events over 24 months of follow up (HR, 0.84; 95% CI, 0.76 to 0.94; P value not reported). In patients with recent ACS, intensive statin therapy was associated with lower cardiovascular mortality over 24 months of follow up (HR, 0.76; 95% CI, 0.66 to 0.87). In patients with recent ACS, intensive statin therapy was associated with lower ischemia over 24 months of follow up (HR, 0.68; 95% CI, 0.50 to 0.92). In patients with recent ACS, intensive statin therapy was not associated with a lower incidence of MIs over 24 months of follow up (HR, 0.89; 95% CI, 0.60 to 1.33). Intensive statin therapy was associated with a significantly greater reduction in LDL-C compared to controls (P<0.001). Adverse effects were similar between the two treatments (P value not reported). Secondary: Not reported
Cannon et al.[197] (2004) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen)	DB, DD, MC, RCT Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI	N=4,162 Up to 3 years (mean 2 years)	Primary: Rates of composite death from any cause, MI, documented unstable angina requiring hospitalization,	Primary: The rates of composite death from any cause, MI, unstable angina requiring hospitalization, revascularization and stroke at two years were 26.3 and 22.4% with pravastatin and atorvastatin, representing a 16% reduction in the HR favoring atorvastatin (95% CI, 5 to 26; P=0.005). Secondary: The risk of death due to CHD, nonfatal MI or revascularization was reduced by 14% with atorvastatin (P=0.029) with a two year event rate of 19.7%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs pravastatin 40 mg/day (standard regimen)	or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL		revascularization and stroke Secondary: Risk of death due to CHD, nonfatal MI or re-vascularization; risk of the individual components of the primary endpoint; discontinuation rates; safety	compared to a two year event rate of 22.3% with pravastatin. The risk of death, MI or urgent revascularization was reduced by 25% with atorvastatin (P<0.001). Among the individual components of the primary endpoint, atorvastatin was associated with a significant reduction of 14% for revascularization (P=0.04) and a 29% reduction in the risk of recurrent unstable angina (P=0.02) compared to pravastatin. There were nonsignificant reductions in the rates of death or MI (18%, P=0.06) and the rates of stroke (P value not reported) between the two treatments. The discontinuation rates due to adverse events or for other reasons were 21.4 and 22.8% with pravastatin and atorvastatin at one year (P=0.30) and 33.0 and 30.4%, respectively at two years (P=0.11). Discontinuation rates due to myalgias or muscle aches or elevations in CK levels were 2.7 and 3.3% with pravastatin and atorvastatin (P=0.23). There were 1.1 and 3.3% of patients receiving pravastatin and atorvastatin who had elevations in ALT levels that were at least three times the upper limit of normal (P<0.001).
Ray et al.[198] (2005) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22 Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within	N=4,162 Up to 3 years (mean, 2 years)	Primary: A composite of all-cause mortality, MI, unstable angina requiring hospitalization, revascularization or stroke Secondary: A composite of death, MI or unstable angina requiring hospitalization	Primary: After 30 days, 3.0 and 4.2% of patients receiving atorvastatin and pravastatin experienced a primary endpoint (HR, 72; 95% CI, 0.52 to 0.99; P=0.046). From six months to the end of the trial, 15.1 and 17.7% of patients receiving atorvastatin and pravastatin experienced a primary endpoint (HR, 82; 95% CI, 0.69 to 0.99; P=0.037). Secondary: Atorvastatin was associated with a significant reduction in the risk of the triple composite endpoint compared to pravastatin (15.7 vs 20.0%; HR, 76; 95% CI, 0.66 to 0.88; P=0.0002). After 30 days, patients receiving atorvastatin experienced a significantly greater reduction in LDL-C and hsCRP level compared to patients receiving pravastatin (P<0.001 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL			
Ahmed et al.[199] (2006) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22 Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained	N=4,162 Up to 3 years (mean, 2 years)	Primary: A composite of death, MI, unstable angina requiring hospitalization, revascularization with PCI or CABG surgery occurring within 30 days after randomization or stroke within two years after trial onset Secondary: A composite of death, MI or unstable angina requiring	Primary: There was no significant difference between the two treatments in terms of the primary endpoint among patients with diabetes (31.8 vs 28.4%; HR, 88; P=0.28). Secondary: Atorvastatin was associated with a significantly lower rate for the secondary composite endpoint compared to pravastatin among patients with diabetes (21.1 vs 26.6%; HR, 0.75; P=0.03) and patients without diabetes (14 vs 18%; HR, 0.76; P=0.002). Consequently, treating 1,000 diabetic and nondiabetic patients with atorvastatin would prevent 55 and 40 events, respectively (P value not reported). Compared to nondiabetic patients, fewer patients with diabetes receiving atorvastatin achieved the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L (37.6 vs 45.4%; P=0.004). Out of diabetic patients receiving atorvastatin, 62% failed to reach the dual goal of LDL-C <70 mg/dL and hsCRP <2 mg/L.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL, stratified by type 2 diabetes		hospitalization; LDL-C <70 mg/dL goal; hsCRP <2 mg/L goal; MI; unstable angina requiring hospitalization	Diabetic patients who reached the dual LDL-C and CRP goals had significantly lower rates of the secondary endpoint compared to patients who failed to reach the goal (17.7 vs 24.7%; P=0.021). In the diabetic population, among the individual components of the primary and secondary composite endpoints, the only variable exhibiting a significant reduction with atorvastatin compared to pravastatin was unstable angina requiring hospitalization (3.1 vs 7.4%; P=0.003).
Scirica et al.[200] (2006) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22 Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-	N=4,162 Up to 3 years (mean, 2 years)	Primary: Hospitalization for heart failure occurring ≥30 days after randomization Secondary: Not reported	Primary: Atorvastatin was associated with a significant reduction in the rate of hospitalization for heart failure compared to pravastatin (1.6 vs 3.1%; HR, 0.55; 95% CI, 0.35 to 0.85; P=0.008). The benefit observed with atorvastatin was independent on recurrent MI or prior history of heart failure. Higher BNP was associated with an increased risk for heart failure (HR, 2.6; 95% CI, 1.2 to 5.5; P=0.016). Among patients with a high BNP level (>80 pg/mL), atorvastatin was associated with a lower incidence of heart failure compared to pravastatin (HR, 0.32; 95% CI, 0.13 to 0.8; P=0.014). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL			
Ray et al.[201] (2006) PROVE IT-TIMI 22 Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	Subanalysis of PROVE IT-TIMI 22 Patients ≥18 years of age in stable condition after a hospitalization for an ACS with either an acute MI or high risk unstable angina in the preceding 10 days, with TC ≤240 mg/dL measured within the first 24 hours after the onset of the ACS or up to 6 months earlier if no sample had been obtained during the first 24 hours; patients who were receiving long-term lipid-lowering therapy at the time of the ACS had a TC ≤200 mg/dL, stratified by age	N=4,162 Up to 3 years (mean, 2 years)	Primary: Cardiac mortality; MI; unstable angina requiring hospitalization; relationship between NCEP goal and a composite primary endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, re-vascularization or stroke Secondary: A composite of death, MI or unstable angina requiring hospitalization	Primary: At 30 days, a greater proportion of patients in both age groups receiving atorvastatin achieved the NCEP goals compared to patients in both age groups receiving pravastatin (P<0.001). Among patients ≥75 years of age, the achievement of the NCEP LDL-C goal was associated with an eight percent reduction in the risk of primary endpoint from baseline (P=0.008). The younger age group achieving the NCEP LDL-C goal was associated with a 2.3% reduction in the risk of primary endpoint from baseline (P=0.013). Patients <75 years of age were associated with a lower risk of the primary composite endpoint compared to patients ≥75 years of age (23.0 vs 30.4%; P<0.0001). Patients <75 years of age were associated with a lower risk of all-cause mortality (P<0.0001), MIs (P<0.0001), unstable angina requiring hospitalization (P=0.01) or strokes (P=0.004) compared to patients ≥75 years of age. Secondary: The composite triple endpoint occurred more frequently in patients ≥75 years of age (20.1 vs 11.0%; HR, 1.93; 95% CI, 1.59 to 2.33; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	(<75 years of age and ≥75 years of age)			
Deedwania et al.[202] (2007) SAGE Atorvastatin 80 mg/day (intensive regimen) vs pravastatin 40 mg/day (standard regimen)	DB, DD, MC, PG, RCT Ambulatory patients 65 to 85 years of age with CAD, ≥1 episode of myocardial ischemia that lasted ≥3 minutes during a 48 hour ambulatory ECG at screening and baseline LDL-C 100 to 250 mg/dL	N=893 12 months	Primary: Absolute change from baseline in the total duration of myocardial ischemia on 48 hour Holter monitor Secondary: Absolute change from baseline to month three in the total duration of myocardial ischemia on 48 hour Holter monitor; percent change from baseline to months three and 12 in the total duration of myocardial ischemia; absolute and percent changes from baseline to months three and 12 in the number of	Primary: After 12 months, the total duration of ischemia was significantly reduced from baseline with both treatments (P<0.001). There was no significant difference between the two treatments in terms of the primary endpoint (P=0.88). Secondary: There were no significant differences between the two treatments in any of the secondary endpoints assessing degree of ischemia at months three and 12 (P value not reported). Atorvastatin was associated with a significant 77% reduction in all-cause mortality compared to pravastatin (HR, 0.33; 95% CI, 0.13 to 0.83; P=0.014). Compared to pravastatin, atorvastatin was associated with significantly greater reductions in TC, LDL-C, TG and apo B at months three and 12 (P<0.001). Compared to atorvastatin, pravastatin was associated with a significantly greater increase in HDL-C at three (P<0.001) and 12 months (P=0.009). Atorvastatin was associated with a significantly higher incidence of liver test abnormalities (17.3 vs 13.9%; P<0.001). There were no significant differences between pravastatin and atorvastatin in treatment related adverse events (13.9 vs 17.3%; P=0.17).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			ischemic episodes; percent change in ischemic burden; proportion of patients free of ischemia at months three and 12; percent changes in the levels of TC, LDL-C, HDL-C, TG and apo B	
Pitt et al.[203] (2012) LUNAR Atorvastatin 80 mg/day vs rosuvastatin 20 mg/day vs rosuvastatin 40 mg/day	MC, OL, PG, PRO, RCT Patients 18 to 75 years of age with CAD who were hospitalized for ACS within 48 hours of ischemic symptoms with non-ST-segment elevation ACS or ST-segment elevation ACS who received optimal reperfusion therapy (successful treatment with a thrombolytic agent or primary	N=825 12 weeks	Primary: Averaged LDL reduction measurements at six and 12 weeks Secondary: Percentage reduction from baseline in LDL at two, six and 12 weeks, percentage change in TC, HDL, apo AI, apo B, LDL:HDL cholesterol, TC/HDL, non-HDL:HDL-C, apo B:apo AI,	Primary: The averaged week six and 12 LDL reduction from baseline was significantly greater with rosuvastatin 40 mg compared to atorvastatin 80 mg (46.8 vs 42.7%; P<0.05). The reduction from baseline with rosuvastatin 20 mg was -42.0%. Secondary: Compared to treatment with atorvastatin 80 mg, LDL was significantly reduced with rosuvastatin 20 mg at two weeks (P<0.01) and weeks six through 12 (P<0.05 for both). Similarly, rosuvastatin 40 mg significantly lowered LDL compared to atorvastatin 80 mg at weeks two, six and 12 (P<0.01 for all). The percent change in TC was significantly greater with rosuvastatin 20 mg compared to atorvastatin 80 mg (-28.6 vs 30.9%; P<0.05). Rosuvastatin 40 mg reduced TC from baseline by 32.2%. Both the 20 and 40 mg dose of rosuvastatin significantly increased HDL compared to atorvastatin 80 mg (9.7 and 11.9 vs 5.6%; P<0.01 for both rosuvastatin doses). Apo AI was significantly higher following treatment with rosuvastatin 20 and 40 mg compared to atorvastatin 80 mg (10.3 and 10.1 vs 4.2, respectively;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	catheter-based intervention initiated within 12 hours of symptom onset), LDL cholesterol level >70 mg/dL and a fasting TG level <500 mg/dL within 72 hours of symptom onset		change in CRP at six and 12 weeks and safety	P<0.01 for both rosuvastatin doses). There were no statistically significant differences between either dose of rosuvastatin and atorvastatin 80 mg with regard to decrease in Apo B over 12 weeks. The ratio of LDL:HDL decreased in all three groups, however, rosuvastatin 40 mg was associated with a greater percentage reduction compared to atorvastatin 80 mg (-51.5 vs 44.5%; P<0.001). Rosuvastatin 40 mg significantly reduced the ratio of TC:HDL compared to atorvastatin 80 mg (-38.2 vs 33.1%; P<0.001). Rosuvastatin 20 mg reduced the TC/HDL ratio by 34.0%. Rosuvastatin 40 mg also significantly improved the ratio of non-HDL:HDL compared to atorvastatin 80 mg (-47.3 vs -41.2%; P<0.001). Rosuvastatin 20 mg reduced the non-HDL:HDL ratio by -42.3%. The ratio of apo B:apo AI was significantly reduced with rosuvastatin 40 mg compared to atorvastatin 80 mg (P<0.001). The percent change in CRP at week 12 was >80% in all groups; however, there was no statistically significant difference between the treatments.
Pedersen et al.[204] (2005) IDEAL Atorvastatin 80 mg/day vs simvastatin 20 to 40 mg/day	MC, OL, PG, RCT Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines	N=8,888 4.8 years	Primary: Incidence of a major coronary event (CHD death, nonfatal MI or cardiac arrest with resuscitation) Secondary: Major cardiovascular events (any primary event	Primary: Atorvastatin was associated with a nonsignificant reduction in the risk of a major coronary event compared to simvastatin (9.3 vs 10.4%; HR, 0.89; P=0.07). Secondary: Atorvastatin was associated with a significant reduction in the risk of a nonfatal MI compared to simvastatin (6.0 vs 7.2%; HR, 0.83; P=0.02). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; P=0.02). Atorvastatin was associated with a significant reduction in the risk of any

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			plus stroke), any CHD event (any primary event, any coronary revascularization procedure or hospitalization for unstable angina), any cardiovascular events (any of the former plus hospitalization with a primary diagnosis of CHF and PAD), all individual endpoints, all-cause mortality	CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; P<0.001). Atorvastatin was associated with a significant reduction in the risk of any cardiovascular events compared to simvastatin (26.5 vs 30.8%; HR, 0.84; P<0.001). Atorvastatin was associated with a significant reduction in the risk of peripheral vascular disease compared to simvastatin (2.9 vs 3.8%; HR, 0.76; P=0.02). Atorvastatin was associated with a nonsignificant reduction in the risk of fatal or nonfatal stroke compared to simvastatin (3.4 vs 3.9%; HR, 0.87; P=0.20). Atorvastatin was associated with a nonsignificant reduction in the risk of hospitalization for nonfatal heart failure compared to simvastatin (2.2 vs 2.8%; HR, 0.81; P=0.11). Atorvastatin was associated with a nonsignificant reduction in the risk of death from cardiovascular or noncardiovascular cause compared to simvastatin (4.9 vs 5.0; HR, 1.03; 95% CI, 0.85 to 1.24; P=0.78 and 3.2 vs 3.5%; HR, 0.92; P=0.47). Atorvastatin was associated with a nonsignificant reduction in the risk of all-cause mortality compared to simvastatin (8.2 vs 8.4%; HR, 0.98; P=0.81). Atorvastatin was associated with a higher rate of drug discontinuations due to adverse effects compared to simvastatin (9.6 vs 4.2%; P<0.001). Atorvastatin was associated with a higher rate of liver transaminase elevations compared to simvastatin (P<0.001). There was no significant difference between the two treatments in the incidence of serious adverse events (P=0.42).
Tikkanen et al.[205] (2009) IDEAL	Post hoc analysis of IDEAL	N=8,888 4.8 years	Primary: Incidence of a major coronary	Primary: There was no significant heterogeneity of treatment effect by age for any composite endpoint, indicating that the benefit of atorvastatin was similar for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Atorvastatin 80 mg/day vs simvastatin 20 to 40 mg/day	Adult patients with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines; stratified by age (<65 years of age vs ≥65 years of age)		event (coronary death, confirmed nonfatal acute MI or cardiac arrest with resuscitation) Secondary: Major cardiovascular events (any primary event and stroke), any CHD event (any primary event, any coronary re-vascularization procedure, any hospitalization for unstable angina), any cardiovascular events	younger and older patients. Nevertheless, the cardiovascular risk reductions associated with atorvastatin tended to be numerically lower in the older than younger age group. Atorvastatin was associated with a 20% decrease in risk of the primary endpoint of major coronary events in patients <65 years of age (HR, 0.80; 95% CI, 0.66 to 0.98), with similarly significant reductions in secondary composite endpoints. Secondary: There were similarly significant reductions in secondary composite endpoints, the corresponding reductions in the risk in patients ≥65 years of age were four to 12%, and significance was achieved for only the endpoint of any cardiovascular event in older patients (HR, 0.88; 95% CI, 0.79 to 0.99).
Strandberg et al.[206] (2009) IDEAL Atorvastatin 80 mg/day vs simvastatin 20 mg/day	Post hoc analysis of IDEAL Patients ≤80 years of age with a history of an MI and qualifying for statin therapy based on NCEP ATP III guidelines	N=8,888 4.8 years	Primary: Hospitalization for heart failure Secondary: Not reported	At baseline, a history of heart failure (NYHA class I to IIIa) was reported by 537 patients, 5.5 (n=244) and 6.6% (n=293) of patients receiving simvastatin and atorvastatin, respectively. Primary: During the trial, there were 222 new hospitalizations for heart failure. Incidences of hospitalization for heart failure were 10.6 (57/537) vs 2.0% (165/8,351) in patients with and without a history of heart failure. Of the new cases, most were not preceded by an in-trial MI. Of the 222 patients with new hospitalization for heart failure during the trial, 71 (32.0%) patients subsequently died. Among the 222 new hospitalizations, 123 (2.8%) occurred with simvastatin compared to 99 (2.2%) with atorvastatin (HR, 0.81; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				0.62 to 1.05; P=0.11). Of the 537 patients with heart failure at baseline, 104 died during the trial compared to 36 of the patients without a history of heart failure (HR, 2.66; 95% CI, 2.16 to 3.27; P<0.0001). After adjustments in the entire trial cohort, atorvastatin was associated with a 26% decrease (P=0.03) of new or recurrent heart failure events compared to simvastatin. Atorvastatin tended to be associated with fewer recurrent heart failure events in those with heart failure at baseline (n= 537; P=0.11) and in those without heart failure at baseline (n=8,351; P=0.15). Secondary: Not reported
Sakamoto et al.[207] (2007) MUSASHI-AMI Lipophilic statins (mean daily doses; atorvastatin 9.3 mg, fluvastatin 26.8 mg, pitavastatin 2 mg, simvastatin 5 mg) vs hydrophilic statin (mean daily dose; pravastatin 9.4 mg) All medications were administered within 96 hours of	MC, RCT Adult patients randomized to statin or no statin therapy within 96 hours of an acute MI, with TC 190 to 240 mg/dL	N=486 416 days	Primary: Composite of ACS events (cardiovascular death, nonfatal MI, recurrent acute myocardial ischemia requiring emergency hospitalization) Secondary: Incidence of individual components of the primary endpoint, nonfatal stroke, heart failure requiring emergent	Primary: Hydrophilic statin therapy was associated with a nonsignificant lower incidence of ACS events compared to lipophilic statin therapy (3.6 vs 9.9%; P=0.053). Secondary: Hydrophilic statin therapy was associated with a significantly lower incidence of new Q-wave appearance on the ECG compared to lipophilic statin therapy (75% vs 89%; P=0.0056). There was no difference between the two treatments in any of the other secondary endpoints (P=0.339).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
hospital admission with an acute MI.			rehospitalization, new Q-wave appearance on the ECG	
Afilalo et al.[208] (2007) Moderate statin therapy (pravastatin ≤40 mg/day, lovastatin ≤40 mg/day, fluvastatin ≤40 mg/day, simvastatin ≤20 mg/day, atorvastatin ≤10 mg/day, rosuvastatin ≤5 mg/day) vs intensive statin therapy (simvastatin 80 mg/day, atorvastatin 80 mg/day, rosuvastatin 20 to 40 mg/day)	MA (6 RCTs) Patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=28,505 ≥6 months	Primary: All-cause mortality, CHD mortality, hospitalization for heart failure, major coronary event (cardiovascular death or ACS), stroke, adverse effects Secondary: Not reported	Primary: In patients with recent ACS, intensive statin therapy was associated with lower all-cause mortality (OR, 0.75; 95% CI, 0.61 to 0.93). By treating 90 people with intensive statin therapy, one death could be prevented. All-cause mortality was not reduced by intensive statin therapy among patients with stable CHD (OR, 0.99; 95% CI, 0.89 to 1.11). In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.86; 95% CI, 0.73 to 1.01). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of major coronary events (OR, 0.82; 95% CI, 0.75 to 0.91). Treating 46 patients with intensive statin therapy may prevent one major coronary event. In patients with recent ACS, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.63; 95% CI, 0.46 to 0.86). In patients with stable CHD, intensive statin therapy was associated with a reduction in the incidence of heart failure hospitalizations (OR, 0.77; 95% CI, 0.64 to 0.92). Treating 112 patients with intensive statin therapy may prevent one hospitalization for heart failure. Intensive statin therapy was associated with a threefold increase in adverse hepatic (OR, 3.73; 95% CI, 2.11 to 6.58) and muscular events (OR, 1.96; 95% CI, 0.50 to 7.63). Consequently, 96 people would need to be treated, for one

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				patient to experience an adverse hepatic event. Secondary: Not reported
Cannon et al.[209] (2006) Intensive statin therapy (simvastatin 40 to 80 mg/day, atorvastatin 80 mg/day) vs moderate statin therapy (pravastatin 40 mg/day, simvastatin 20 mg/day, atorvastatin 10 mg/day)	MA (4 RCTs) Patients with recent ACS or stable CHD randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)	N=27,548 (4 studies) Up to 5 years	Primary: Combined incidence of coronary death or nonfatal MI; the combined incidence of coronary death or any cardiovascular event (MI, stroke, hospitalization for unstable angina or re-vascularization); incidence of stroke; incidence of cardiovascular, noncardiovascular and all-cause mortality Secondary: Not reported	Primary: Intensive statin therapy was associated with a significant odds reduction of 16% for coronary death or MI compared to moderate statin therapy (9.4 vs 8.0%; OR, 0.84; 95% CI, 0.77 to 0.91; P<0.00001). Intensive statin therapy was associated with a significant odds reduction of 16% for coronary death or any cardiovascular event compared to moderate statin therapy (32.3 vs 28.8%; OR, 0.84; 95% CI, 0.80 to 0.89; P<0.0000001). Intensive statin therapy was associated with a nonsignificant reduction in cardiovascular mortality of 12% compared to moderate statin therapy (3.8 vs 3.3%; OR, 0.88; 95% CI, 0.78 to 0.1.00; P=0.054). Intensive statin therapy was associated with a nonsignificant lower rate of noncardiovascular mortality compared to moderate statin therapy (P=0.73). Intensive statin therapy was associated with a nonsignificant significant reduction in all-cause mortality compared to moderate statin therapy (6.2 vs 5.9%; P=0.20). Intensive statin therapy was associated with a significant overall odds reduction of 18% for stroke compared to moderate statin therapy (2.8 vs 2.3%; OR, 0.82; 95% CI, 0.71 to 0.96; P=0.012). Intensive statin therapy was associated with a significant odds reduction of 16.5% for CHD death or MI compared to moderate statin therapy (OR, 0.835; 95% CI, 0.77 to 0.91; P<0.0001). Secondary: Not reported
Murphy et al.[210] (2007)	MA (2 RCTs) Patients with	N=8,658 Up to 2 years	Primary: Incidence of cardiovascular,	Primary: Intensive statin therapy was associated with a significant 23% reduction in the risk of all-cause mortality compared to moderate statin therapy (3.6 vs 4.9%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Intensive statin therapy (simvastatin 40 to 80 mg/day, atorvastatin 80 mg/day) vs moderate statin therapy (pravastatin 40 mg/day, simvastatin 20 mg/day)	recent ACS, clinically stable for 12 to 24 hours, randomized to an intensive statin therapy (intervention) or moderate statin therapy (control)		non-cardiovascular and all-cause mortality Secondary: Not reported	HR, 0.77; 95% CI, 0.63 to 0.95; P=0.015). Intensive statin therapy was associated with a significant 24% reduction in the risk of cardiovascular mortality compared to moderate statin therapy (2.6 vs 3.5%; HR, 0.76; 95% CI, 0.59 to 0.97; P=0.025). Intensive statin therapy was associated with a nonsignificant reduction in the risk of noncardiovascular mortality compared to moderate statin therapy (1.0 vs 1.4%; HR, 0.82; 95% CI, 0.55 to 1.21; P=0.32). Secondary: Not reported
Combination Products				
Hypercholesterolemia (Combination Products)				
Erdine et al.[211] (2009) Gemini-AALA Amlodipine-atorvastatin 5- or 10-10, 20, 40 or 80 mg/day All possible dosing combinations were evaluated. Patients were classified into 1 of 3 cardiovascular risk categories.	OL, PRO Patients 18 to 80 years of age with concurrent HTN and dyslipidemia	N=1,649 14 weeks	Primary: Proportion of patients achieving both BP and LDL-C goals Secondary: Absolute and percentage change from baseline in BP and lipid levels, BP and LDL-C goal attainment stratified by prior anti-hypertensive and lipid	Primary: More than half (55.2%) of patients achieved both their BP and LDL-C goals at the end of 14 weeks. A higher proportion of patients in Groups 1 and 2 achieved both goals compared to patients in Group 3 (81.3 and 78.8 vs 40.3%). When patients in Group 3 without diabetes (n=407) were further analyzed using a BP goal <140/90 mm Hg, goal achievement for both BP and LDL-C in nondiabetic patients rose to 70.0%. Secondary: All doses achieved significant improvements in LDL-C, TG, HDL-C, TC, SBP and DBP (P<0.001 for all). The proportions of patients with no prior treatment for HTN and dyslipidemia in the cardiovascular risk categories were 74.1 (95% CI, 53.7 to 88.9), 81.6 (95% CI, 72.7 to 88.5) and 39.8% (95% CI, 30.0 to 50.2) for Groups 1, 2 and 3. The corresponding proportions for patients with prior treatment for HTN and dyslipidemia were 82.0 (95% CI, 68.6 to 91.4), 80.7 (95% CI, 73.1 to 87.0) and 39.5% (95% CI, 35.3 to 43.8). The corresponding proportions for patients with no prior treatment for dyslipidemia were 80.2 (95% CI, 69.9 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Group 1: HTN and dyslipidemia with no additional cardiovascular risk factors (BP goal: <140/90 mm Hg, LDL-C goal: <4.1 mmol/L). Group 2: HTN and dyslipidemia with ≥1 additional cardiovascular risk factor, excluding CHD and diabetes (BP goal: <140/90 mm Hg, LDL-C goal: <3.4 mmol/L). Group 3: HTN and dyslipidemia with CHD or CHD risk equivalent (diabetes or other atherosclerotic disease (BP goal: <130/80 mm Hg, LDL-C goal: <2.6 mmol/L).			lowering medications	88.3), 77.8 (95% CI, 73.0 to 82.2) and 40.9% (95% CI, 36.1 to 45.7). The corresponding proportions for patients with prior treatment for dyslipidemia were 82.8 (95% CI, 70.6 to 91.4), 80.9 (95% CI, 73.8 to 86.8) and 39.8% (95% CI, 35.9 to 43.9). The corresponding proportions for patients with no prior treatment for HTN were 77.1 (95% CI, 59.9 to 89.6), 81.7 (95% CI, 73.6 to 88.1) and 41.1% (95% CI, 33.1 to 49.3). The corresponding proportions for patients with prior treatment for HTN were 82.7 (95% CI, 74.0 to 89.4), 77.9 (95% CI, 73.3 to 82.0) and 40.1% (95% CI, 36.8 to 43.5). The corresponding proportions for patients with prior treatment for HTN only were 83.3 (95% CI, 70.7 to 92.1), 76.2 (95% CI, 70.2 to 81.5) and 41.2% (95% CI, 35.8 to 46.8). The corresponding proportions of patients with prior treatment for dyslipidemia only were 87.5 (95% CI, 47.3 to 99.7), 82.4 (95% CI, 56.6 to 96.2) and 43.4% (95% CI, 29.8 to 57.7).
Flack et al.[212] (2008) CAPABLE Amlodipine-	MC, OL African American patients 18 to 80 years of age with	N=489 20 weeks	Primary: Proportion of patients in three cardiovascular risk groups	Primary: More patients in Groups 1 and 2 achieved both goals compared to patients in Group 3 (69.7, 66.7 and 28.2%, respectively; P value not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
atorvastatin 5- or 10-10, 20, 40, or 80 mg/day All possible dosing combinations were evaluated.	uncontrolled HTN and dyslipidemia		(Group 1: patients without additional risk factors; Group 2: patients with >1 additional risk factors, excluding CHD and diabetes and Group 3: patients with CHD or CHD risk equivalent) who achieved the JNC 7 and NCEP ATP III goals Secondary: Changes from baseline in SBP, DBP, LDL-C, TC, TG, HDL-C and apo B	Combination therapy was associated with a 17.5 and 10.1 mm Hg decrease in the SBP and DBP, respectively (P value not reported). Combination therapy was associated with a 23.6% reduction in LDL-C (P value not reported). Combination therapy was associated with a 17% reduction in TC (P value not reported). Combination therapy was associated with a 2.2% increase in HDL-C (P value not reported). Combination therapy was associated with a 6.9% reduction in TG (P value not reported). Combination therapy was associated with a 19.3% reduction in apo B (P value not reported).
Hobbs et al (abstract).[213] (2009) Amlodipine-atorvastatin 5- or 10-10, 20, 40 or 80 mg/day All possible dosing combinations	2 MC, OL Patients with uncontrolled BP and controlled/uncontrolled LDL-C qualifying for treatment according to local governing guidelines	N=2,245 16 weeks	Primary: Proportion of patients achieving country-specific BP and LDL-C goals, safety Secondary: Not reported	Primary: Within the two trials, 62.9 and 50.6% of patients achieved both country-specific BP and LDL-C goals. BP was reduced by 20.4/10.7 and 21.8/12.6 mm Hg in the two trials, respectively, and reductions in LDL-C were 34.8 and 42.2 mg/dL, respectively. The most common adverse events were peripheral oedema (11.0%), joint swelling (2.9%) and headache (2.9%), of which, only oedema was linked to trial medication. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
were evaluated.				
Neutel et al.[214] (2009) CUSP Amlodipine-atorvastatin 5-20 mg/day vs placebo All patients also received lifestyle changes. After 4 weeks, add-on antihypertensive and/or lipid lowering therapy was permitted.	DB, MC, PC, RCT Patients ≥21 years of age with coexisting HTN (140 to 168/90 to 105 mm Hg) and dyslipidemia (LDL-C 110 to 160 mg/dL), without a history of cardiovascular disease who have never received treatment in the 3 months prior to enrollment	N=130 8 weeks	Primary: Proportion of patients who achieved both BP (<140/90 mm Hg) and LDL-C (<100 mg/dL) goals at week four Secondary: Proportion of patients who achieved both BP and LDL-C goals at week eight; proportion of patients who achieved both BP and LDL-C goals at both weeks four and eight; proportion of patients who achieved the LDL-C goal at weeks four and eight; mean changes from baseline in SBP, DBP and LDL-C at weeks four and eight; 10 year	Primary: After four weeks, the proportion of patients who achieved both BP and LDL-C goals was significantly greater with combination therapy compared to placebo (47.6 vs 1.7%; OR, 59.8; 95% CI, 7.4 to 486.0; P<0.001). Secondary: After eight weeks, the proportion of patients who achieved both BP and LDL-C goals was significantly greater with combination therapy compared to placebo (55.6 vs 5.0%; OR, 23.8; 95% CI, 6.7 to 85.0; P<0.001). After four and eight weeks, the proportion of patients who achieved the BP goal was significantly greater with combination therapy compared to placebo (P=0.001 and P=0.006). After four and eight weeks, the proportion of patients who achieved the LDL-C goal was significantly greater with combination therapy compared to placebo (P<0.001 for both). Mean reductions in SBP (13.3 vs 5.6 mm Hg) and DBP (9.4 vs 4.2 mm Hg) at week four was significantly greater with combination therapy (P<0.001). The mean percentage change in LDL-C (35.6 vs +3.3%) at week four was significantly greater with combination therapy (P<0.001). These benefits were maintained throughout eight weeks of treatment. With placebo, 10 year Framingham risk of CHD increased by 4.1% both at weeks four and eight relative to baseline. With combination therapy, the risk of future cardiac events over the next 10 years decreased by 33 and 38% at weeks four and eight, respectively, relative to baseline (P<0.001 vs placebo).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			Framingham risk of CHD at weeks four and eight	
Grimm et al.[215] (2010) TOGETHER Amlodipine-atorvastatin 5- to 10-20 mg/day vs amlodipine 5 to 10 mg/day All patients received therapeutic lifestyle changes.	DB, DD, PRO, RCT Patients ≥21 years of age with HTN, no history of cardiovascular disease or diabetes and ≥2 of the following risk factors: age ≥45 years if male and ≥55 years if female; current smoker; a family history of premature CHD in a first-degree relative; HDL-C <40 mg/dL; waist circumference 102 cm if male or 88 cm if female; all patients had been previously treated with amlodipine 5 or 10 mg with either controlled or Stage 1 HTN, fasting LDL-C ≥100 to ≤170 mg/dL	N=245 6 weeks	Primary: Proportion of patients achieving both BP (<140/90 mm Hg) and LDL-C (<100 mg/dL) goals Secondary: Proportion of patients achieving both BP and LDL-C goals at four weeks; proportion of patients achieving the BP or LDL-C goal at weeks four and six; change from baseline in SBP, DBP, LDL-C, TC, TG and HDL-C at four and six weeks; predicted 10 year Framingham risk of CHD	Primary: The proportion of patients achieving both BP and LDL-C goals at six weeks was 67.8 vs 9.6% with combination therapy and amlodipine (risk difference, 58.2; 95% CI, 48.1 to 68.4; P<0.001; OR, 19.0; 95% CI, 9.1 to 39.6; P<0.001). Secondary: The proportion of patients achieving both BP and LDL-C goals at four weeks was 62.9 vs 5.2% (risk difference, 57.7; 95% CI, 47.9 to 67.5; P<0.001; OR, 31.4; 95% CI, 12.6 to 78.1; P<0.001). LDL-C goal was achieved by 82.8 and 7.0% (risk difference, 75.8; 95% CI, 67.4 to 84.2; P<0.001; OR, 65.5; 95% CI, 27.1 to 158.3; P<0.001) at four weeks and 83.9 and 11.3% (risk difference, 72.6; 95% CI, 63.7 to 81.5; P<0.001; OR, 42.0; 95% CI, 19.4 to 91.0; P<0.001) at six weeks. The difference in the proportions of patients achieving the BP goal at weeks four and six were not significantly different between the two treatments (four weeks; OR, 1.1; P=0.785 and six weeks; OR, 1.5; P=0.171). There were significant mean percentage reductions from baseline in LDL-C, TC and TG with combination therapy compared to amlodipine at four and six weeks (P<0.001 for all comparisons). There was no difference in DBP between the two treatments and no difference in SBP at week four; however, at week six improvements in SBP were significantly greater with combination therapy compared to amlodipine (P=0.02). In patients receiving combination therapy, the 10 year Framingham risk for CHD at baseline was 8.2% and was reduced to 5.5 and 5.4% at weeks four and six compared to amlodipine (remained unchanged, 8.1%) (P<0.001). After four weeks, the percentage relative reduction from baseline in the 10 year Framingham risk for CHD in patients receiving combination therapy was 39.6% compared to 0.6% with amlodipine. After six weeks, the corresponding numbers were 42.0 and 4.5% (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
			outcomes at four and six weeks; safety	There were no deaths or serious adverse events reported during the trial. Overall, treatment-related adverse events occurred in 9.0 and 14.8% in patients receiving combination therapy and amlodipine, respectively. The majority of events with both treatments were mild. Changes in liver function test and creatinine phosphokinase were mild to moderate.
Bays et al.[216] Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day vs placebo	DB, MC, RCT Patients 18 to 80 years of age with primary hypercholesterolemia with LDL-C >145 but ≤150 mg/dL and TG ≤350 mg/dL	N=1,528 24 weeks	Primary: Percent change from baseline in LDL-C Secondary: Mean and percent changes from baseline in TC, TG, HDL-C, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B, apo AI and hsCRP; proportion of patients reaching their NCEP ATP III LDL-C goal of <130, <100 or <70 mg/dL at 12 weeks	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to simvastatin (53 vs 39%; P<0.001) and ezetimibe (53 vs 18.9%; P<0.001). Secondary: At each corresponding dose of simvastatin, combination therapy was associated with a significant reduction in LDL-C at 12 weeks (P<0.001). Combination therapy was associated with a significant reduction in LDL-C at 12 weeks compared to the next highest dose of simvastatin (P<0.001). Averaged across all doses, combination therapy resulted in a greater proportion of patients reaching their NCEP ATP III LDL-C goal <130, <100 or <70 mg/dL at 12 weeks compared to simvastatin (92.2, 78.6 and 38.7 vs 79.2, 45.9 and 7.0%, respectively; P<0.001 for al). Averaged across all doses, combination therapy was associated with a significant reduction in TC, TG, LDL-C:HDL-C, TC:HDL-C, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). Averaged across all doses, combination therapy was not associated with a significant change in HDL-C compared to simvastatin (P=0.607). Treatment-related adverse effects were similar in the pooled simvastatin, combination and ezetimibe groups, but were more frequent than placebo (14.8, 15.1, 12.8 and 8.1%, respectively; P values not reported).
Ose et al.[217] (2007) Simvastatin 10,	DB, MC, RCT Patients 22 to 83 years of age with	N=1,037 14 weeks	Primary: Change from baseline in LDL-C level,	Primary: Across all doses, combination therapy was associated with a significant reduction in LDL-C compared to simvastatin (53.7 vs 38.8%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
20, 40 or 80 mg/day vs ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs ezetimibe 10 mg/day vs placebo	primary hyper-cholesterolemia (LDL-C 145 to 250 mg/dL and TG <350 mg/dL)		TG, TC, non-HDL, hsCRP, LDL-C:HDL-C and TC:HDL-C; proportion of patients reaching LDL-C target (<100 or <70 mg/dL) Secondary: Not reported	Across all doses, combination therapy was associated with a significant reduction in TG, TC, non-HDL, hsCRP, LDL-C:HDL-C and TC:HDL-C compared to simvastatin (P<0.001 for all). A significantly greater proportion of patients receiving combination therapy achieved LDL-C <100 mg/dL compared to simvastatin (79.2 vs 47.9%; P<0.001). Similar results were observed with a LDL-C goal <70 mg/dL (30.4 vs 7.0%; P<0.001). The incidence of drug-related adverse effects was similar with combination therapy and simvastatin (7.4 vs 5.5%, respectively; P value not reported). Secondary: Not reported
Feldman et al.[218] (2006) Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs simvastatin 10, 20, 40 or 80 mg/day vs ezetimibe 10 mg/day	MA (3 DB, PC, RCTs) Patients with primary hypercholesterolemia	N=3,083 28 weeks	Primary: Percent change from baseline in LDL-C, TG, non-HDL-C, apo B and hsCRP; achievement of LDL-C <100 mg/dL at week-12 among patients <65 and ≥65 years of age Secondary: Not reported	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C, TG, non-HDL-C, apo B and hsCRP at 12 weeks compared to simvastatin (P<0.001 for all). These affects did not differ between the older and younger patients (P value not reported). Combination therapy and simvastatin produced comparable increases in HDL-C (8 vs 7%, respectively; P value not reported). Significantly more patients, in all age groups, receiving combination therapy, regardless of the dose, achieved an LDL-C level <100 mg/dL at week 12 compared to patients receiving simvastatin (79 vs 42%; P<0.001). Similar results were observed with a LDL-C goal <70 mg/dL (37 vs 6%; P<0.001). Treatment-related adverse effects were similar with simvastatin and combination therapy, regardless of dose used and age group (P values not reported). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs placebo				Not reported
Farnier et al.[219] (2007) Fenofibrate 160 mg/day vs ezetimibe-simvastatin10-20 mg/day plus fenofibrate 160 mg/day vs ezetimibe-simvastatin 10-20 mg/day vs placebo	DB, MC, PA, PC, RCT Patients 18 to 79 years of age with mixed hyperlipidemia and no CHD or CHD risk equivalent disease, or a 10 year CHD risk >20% according to NCEP ATP III criteria	N=611 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Changes from baseline in TC, TG, non-HDL-C, HDL-C, apo AI and apo B	Primary: LDL-C was significantly reduced with triple therapy (-45.8%) compared to fenofibrate (-15.7%; P<0.01) or placebo (-3.5%; P<0.01), but not when compared to combination therapy (-47.1%; P>0.2). Secondary: HDL-C and apo AI were significantly increased with triple therapy (18.7 and 11.1%) compared to combination therapy (9.3 and 6.6%; P<0.01) or placebo (1.1 and 1.6%; P<0.01), but not when compared to fenofibrate (18.2 and 10.8%; P>0.2). TG, non-HDL-C and apo B were significantly reduced with triple therapy compared to all other active treatments (-50.0, -50.5 and -44.7%; P<0.01, respectively).
Farnier et al.[220] (2008) Fenofibrate 160 mg and ezetimibe-simvastatin 10-20 mg QD vs	DB, MC, PC, RCT Patients 18 to 79 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2	N=611 12 weeks	Primary: Percent change in cholesterol associated with lipoprotein subfractions (VLDL-C 1+2 and VLDL-C 3, IDL-C, LDL-C 1 to 4, Lp[a], HDL-C_2 and	Primary: The effects of ezetimibe-simvastatin, fenofibrate, and ezetimibe/simvastatin plus fenofibrate on VLDL subclasses were similar to those for VLDL-C overall. The maximal changes in IDL-C are achieved by ezetimibe-simvastatin with little additional effect of fenofibrate. Significant reductions were observed for all LDL-C subfractions with ezetimibe-simvastatin treatment. When coadministered with fenofibrate, the effects of both treatments were evident. Ezetimibe-simvastatin plus fenofibrate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
fenofibrate 160 mg QD vs ezetimibe-simvastatin 10-20 mg QD vs placebo	diabetes), or CHD risk score >20% (as defined by NCEP ATP III), LDL-C 130 to 220 mg/dL and TG 150 to 500 mg/dL		HDL-C_3, and changes in LDL particle size) Secondary: Not reported	resulted in a pattern of changes that were similar to fenofibrate monotherapy indicating that the change in LDL-C pattern was primarily a function of fenofibrate. There was no significant difference in cholesterol associated with Lp(a) among the treatment groups. Fenofibrate and ezetimibe-simvastatin plus fenofibrate led to similar increases in median HDL-C_2 and HDL-C_3 compared to ezetimibe-simvastatin and placebo. Ezetimibe-simvastatin did not significantly affect LDL particle size. Fenofibrate and ezetimibe-simvastatin plus fenofibrate increased LDL particle size. At the end of the study, the percentages of patients exhibiting LDL size pattern B was 64, 49, 14, and 17% in the placebo, ezetimibe-simvastatin, fenofibrate, and ezetimibe-simvastatin plus fenofibrate groups, respectively. Secondary: Not reported
Robinson et al.[221] (2009) VYMET Ezetimibe-simvastatin 10-20 to 10-40 mg QD vs atorvastatin 10 to 40 mg QD	DB, MC, PG, RCT Patients 18 to 79 years of age with metabolic syndrome and hypercholesterolemia who were at moderately high or high risk for coronary heart disease	N=1,128 6 weeks	Primary: Percentage of change from baseline in LDL-C Secondary: Changes in other lipids, lipoprotein ratios, hsCRP, and attainment of prespecified lipid levels	Primary: After six weeks, the percent change in LDL-C was significantly greater with ezetimibe-simvastatin than with atorvastatin (all dose comparisons, P<0.001). Secondary: The percent of patients who achieved LDL-C <70 mg/dl and the non-HDL-C goal was significantly greater for ezetimibe-simvastatin than for atorvastatin (all dose comparisons, P<0.05). Treatment with ezetimibe-simvastatin led to a significantly greater reduction in TC, non-HDL-C, apo B, and all 4 lipid ratios compared to atorvastatin (all dose comparison, P<0.001). HDL-C cholesterol increased to a greater extent with ezetimibe/simvastatin 10/20 mg compared to atorvastatin 10 mg (P<0.05) and ezetimibe/simvastatin 10/40 mg compared to atorvastatin 40 mg (P<0.01). Changes in triglycerides, VLDL-C, apo AI, and hsCRP were comparable for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				both treatments, except that apo AI was significantly increased with ezetimibe-simvastatin 10-20 mg vs atorvastatin 10 mg (P<0.05). The rates of adverse events were similar for both treatments.
Ballantyne et al.[222] (2005) VYVA Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day	DB, MC, PG, RCT Patients ≥18 years of age with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with ≥2 risk factors conferring a 10 year risk >20% for CHD; with LDL-C ≥130 mg/dL, no CHD or its risk equivalent, and with ≥2 risk factors conferring a 10 year risk of <20% for CHD; with LDL-C ≥160 mg/dL and no CHD or its risk equivalent with <2 risk factors; with LDL-C ≥190 mg/dL, TG ≤350	N=1,902 6 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: Percent change from baseline in LDL-C at each mg-equivalent statin dose comparison, percent change from baseline in HDL-C, proportion of patients achieving NCEP ATP III LDL-C goal (<100 mg/dL)	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (53.4 vs 45.3%; P<0.001). Secondary: Combination therapy (10/20 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 10 (50.6 vs 36.1%; P<0.001) and 20 mg (50.6 vs 43.7%; P<0.001). Combination therapy (10/40 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 40 mg (57.4 vs 48.3%; P<0.001). Combination therapy (10/80 mg) was associated with a significant reduction in LDL-C compared to atorvastatin 80 mg (58.6 vs 52.9%; P<0.001). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to atorvastatin (7.9 vs 4.3%; P<0.001). Averaged across all doses, a significantly greater proportion of patients receiving combination therapy achieved the NCEP ATP III LDL-C goal compared to atorvastatin (89.7 vs 81.1%; P<0.001). Averaged across all doses, a significantly greater proportion of patients with a CHD or a CHD risk equivalent receiving combination therapy achieved the NCEP ATP III LDL-C goals of <100 (85.4 vs 70.0%; P<0.001) and <70 mg/dL (45.3 vs 20.5%; P<0.001) compared to atorvastatin. Averaged across all doses, combination therapy was associated with a significant increase in the risk of ALT and AST elevation greater than three times the upper limit of normal compared to atorvastatin (P=0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	mg/dL, ALT or AST <1.5 times the upper limit of normal, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the upper limit of normal and a HbA_{1c} <9.0% in patients with diabetes			
Ballantyne et al.[223] (2004) Ezetimibe-simvastatin 10-20 mg/day for weeks 1 to 6, titrated to 10-40 mg for weeks 7 to 18, titrated to 10-80 mg for weeks 19 to 24 vs ezetimibe-simvastatin 10-10 mg/day for weeks 1 to 6, titrated to 10-20 mg/day for weeks 7 to 12, titrated to 10-40 mg/day for weeks	DB, MC, RCT Patients ≥18 years of age with a LDL-C at or above drug treatment thresholds established by NCEP ATP III guidelines, with CAD or CAD risk equivalent, or with ≥2 risk factors conferring a 10 year risk >20% for CHD; with LDL-C ≥130 mg/dL, no CHD or its risk equivalent, and with ≥2 risk factors conferring a 10 year risk of	N=788 24 weeks	Primary: Mean percent change from baseline in LDL-C and HDL-C Secondary: Percent change from baseline to the ends of the second and fourth six week treatment periods in LDL-C and HDL-C, safety	Primary: Averaged across all doses, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (52.4 vs 45.1%; P<0.001). Averaged across all doses, combination therapy was associated with a significant increase in HDL-C compared to atorvastatin (12.3 vs 6.5%; P<0.001). Secondary: At the end of treatment period two, combination therapy was associated with a significant reduction in LDL-C compared to atorvastatin (50.2 and 54.3 vs 44.3%, respectively; P≤0.05). At the end of treatment period two, combination therapy (10/40 mg) was associated with a significant increase in HDL-C compared to atorvastatin (12.4 vs 6.9%; P≤0.05). At the end of treatment period four, combination therapy (10/40 mg) was associated with a significant reduction in LDL-C compared to atorvastatin (59.4 vs 52.5%, respectively; P≤0.05). At the end of treatment period four, combination therapy (10/40 mg) was associated with a significant increase in HDL-C compared to atorvastatin (12.3

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
12 to 18, titrated to 10-80 mg/day for weeks 19 to 24 vs atorvastatin 10 mg/day for weeks 1 to 6, titrated to 20 mg/day for weeks 7 to 12, titrated to 40 mg/day for weeks 12 to 18, titrated to 80 mg/day for weeks 19 to 24	<20% for CHD; with LDL-C ≥160 mg/dL and no CHD or its risk equivalent with <2 risk factors; with LDL-C ≥190 mg/dL, TG ≤350 mg/dL, ALT or AST <1.5 times the upper limit of normal, serum creatinine ≤1.5 mg/dL, no active liver disease, CK <1.5 times the upper limit of normal and a HbA_{1c} <9.0% in patients with diabetes			vs 6.5%; P≤0.05). The safety of combination therapy was observed to be similar to that of atorvastatin (P value not reported).
Foody et al.[224] (2010) VYTELD Ezetimibe-simvastatin 10-20 mg/day vs atorvastatin 10 or 20 mg/day AND Ezetimibe-	DB, MC, PG, RCT Patients ≥65 years of age with hyperlipidemia at moderately high risk or high risk (with CHD or CHD risk equivalents) with or without atherosclerotic vascular disease with LDL-C ≥130 mg/dL, TC ≤350	N=1,289 12 week	Primary: Percent change from baseline in LDL-C Secondary: Proportion of patients achieving an LDL-C <70 and <100 mg/dL; percent change from baseline in TC, TG, HDL-C, non-HDL-C, VLDL-C, apo	Primary: Combination therapy achieved significantly greater percent decreases in LDL-C (-54.2 [10/20 mg] vs -39.5 [10 mg] and -46.6% [20 mg] and -59.1 [10/40 mg] vs -50.8% [40 mg]; P<0.001 for all). Secondary: A significantly greater proportion of combination therapy-treated patients achieved an LDL-C goal <70 mg/dL (51.3 [10/20 mg] and 68.2% [10/40mg]; P<0.05) and <100 mg/dL (83.6 and 90.3%; P<0.001). Analysis based on risk demonstrated that a significantly greater proportion of high risk patients reached target LDL-C levels <70 mg/dL with combination therapy compared to atorvastatin (P<0.001 for all comparisons). Combined analysis of LDL-C level attainment based on atherosclerotic vascular disease status (<100 mg/dL for patients without atherosclerotic vascular disease and <70 mg/dL for patients with atherosclerotic vascular disease) demonstrated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 10-40 mg/day vs atorvastatin 40 mg/day	mg/dL, liver transaminases ≤1.5 times the upper limit of normal with no active liver disease and creatinine kinase ≤2 times upper limit of normal		B, apo AI, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, non-HDL-C:HDL-C and hsCRP; safety	that a significantly greater proportion of patients reached the specified target with combination therapy compared to atorvastatin ($P<0.001$ for ezetimibe/simvastatin 10/20 mg vs atorvastatin 10 mg, $P<0.05$ for ezetimibe/simvastatin 10/20 vs atorvastatin 20 mg and ezetimibe/simvastatin 10/40 mg vs atorvastatin 40 mg). Improvements in non-HDL-C, TC, apo B and lipoprotein ratios were significantly greater with combination therapy ($P<0.01$ to $P<0.001$). Only ezetimibe/simvastatin 10/20 mg significantly improved HDL-C ($P<0.001$) levels compared to atorvastatin 20 mg and TG ($P<0.01$) and VLDL-C ($P<0.05$) levels compared to atorvastatin 10 mg. Improvements in apo AI and hsCRP levels did not differ among the various treatments (P values not reported). All doses of ezetimibe/simvastatin and atorvastatin were generally safe and well tolerated. The incidence of adverse events was similar between treatment groups. There were no serious drug-related adverse events observed during the trial.
Polis et al.[225] (2009) Ezetimibe-simvastatin 10-10, 10-20, 10-40 or 10-80 mg/day vs atorvastatin 10, 20, 40 or 80 mg/day or rosuvastatin 10, 20 or 40 mg/day	Post hoc analysis of 2 trials Patients with hypercholesterolemia not attaining NCEP ATP III LDL-C goals in patients with diabetes, metabolic syndrome or neither disease	N=4,861 6 weeks	Primary: Percent change from baseline in LDL-C, proportion of patients achieving individual LDL-C goals Secondary: Safety	Primary: Changes in LDL-C were generally similar regardless of diabetes/metabolic syndrome status or CHD risk strata in both trials. There was a significant effect by dose level in both trials in all condition and risk subgroups ($P<0.001$), with greater reductions observed with higher doses. NCEP ATP III LDL-C goal attainment was lowest in the high risk group with atherosclerotic vascular disease (12 to 64%) and greatest in the moderate and low risk groups (84 to 100%). Secondary: All treatments were generally well tolerated, with overall similar safety regardless of disease and risk level.
Bardini et al.[226] (2010) LEAD	DB, DD, MC, PG, RCT Patients 18 to 75	N=93 6 weeks	Primary: Percent change from baseline in LDL-C	Primary: Combination therapy produced a significantly greater reduction in LDL-C compared to simvastatin 40 mg (-32.2 vs -20.8%; $P<0.01$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Ezetimibe-simvastatin 10-20 mg/day vs simvastatin 40 mg/day	years of age with type 2 diabetes for ≥12 months and documented CHD, or symptomatic peripheral vascular disease, who were taking a stable dose of simvastatin 20 mg/day for 6 weeks with good compliance and LDL-C ≥100 to ≤160 mg/dL		Secondary: Proportion of patients achieving LDL-C <100 mg/dL; percent change from baseline in TC, HDL-C and TG	Secondary: A nonsignificantly greater proportion of patients receiving combination therapy achieved an LDL-C <100 mg/dL (78.4 vs 60.0%; OR, 2.81; P=0.052). Combination therapy produced a significantly greater change compared to simvastatin 40 mg in TC (-20.6 vs -13.2%; P<0.01). Changes in HDL-C (0.85 vs 0.80%) and TG (-8.5 vs -1.8%) were similar between treatments (P values not reported).
Florentin et al.[227] (2011) Ezetimibe-simvastatin 10-10 mg/day vs simvastatin 40 mg/day	OL, RCT Patients with primary hypercholesterolemia with LDL-C levels above those recommended by the NCEP ATP III	N=100 3 months	Primary: Percent change from baseline in small density LDL-C Secondary: Percent change from baseline in lipid parameters, HOMA index and hsCRP	Primary: Both treatments decreased small density LDL-C (-42 vs -46%; P<0.000 vs baseline for both), with no significant difference between the two treatments (P value not reported). Secondary: Both treatments decreased TC (-31 vs -36%), LDL-C (-43 vs -49%), TG (-17 vs -19%), non-HDL-C (-40 vs -46%) and large LDL-C (-40 vs -44%) (P<0.000 vs baseline for all). Both treatments increased LDL particle size (0.5 vs 0.7%; P<0.05 vs baseline for both). Changes in TC, LDL-C and non-HDL-C were significantly greater with combination therapy (P<0.05 for all), while changes in TG, large LDL-C, and LDL particle size were similar (P values not reported). No significant changes were observed in HOMA index with either treatment, and hsCRP decreased by 23% (P<0.05 vs baseline) with both treatments.
Rotella et al.[228] (2010) Ezetimibe-	2 DB, MC, RCT Patients ≥18 to ≤75 years of age	N=93 6 weeks	Primary: Percentage change from baseline in	Primary: Combination therapy resulted in significantly greater reductions in LDL-C, TC and TC:HDL-C (P<0.01 for all); and significantly more patients treated with combination therapy achieved the LDL-C goal <100 mg/dL (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
simvastatin 10-20 mg/day vs simvastatin 40 mg/day	with documented CHD or symptomatic peripheral vascular disease, who were taking a stable dose of simvastatin 20 mg/day for 6 weeks with good compliance		LDL-C; proportion of patients who achieved an LDL-C goal <100 mg/dL Secondary: Safety	Secondary: There was no significant difference in the proportion of patients who reported adverse events between the two treatments (P=0.606). No significant differences between groups were observed in the number and rate of drug related adverse events, which were reported in 9.8 and 6.3% of patients treated with combination therapy and simvastatin 40 mg (P=0.500). There were few discontinuations due to treatment-related adverse events.
Farnier et al.[229] (2009) IN-CROSS Ezetimibe-simvastatin 10-20 mg/day vs rosuvastatin 10 mg/day	AC, DB, MC, PG, RCT Patients 18 to 80 years of age with hypercholesterolemia (LDL-C ≥100 and ≤190 mg/dL) and high cardiovascular risk who were taking a stable dose of none of the following statin medications for ≥6 weeks prior to trial randomization: atorvastatin (10 or 20 mg), fluvastatin (80 mg), pravastatin (40 mg), rosuvastatin (5 mg) or simvastatin (20 or	N=618 6 weeks	Primary: Percent change from baseline in LDL-C, HDL-C, non-HDL-C, TC, TG and apo B; proportion of patients achieving LDL-C <100 and <70 mg/dL Secondary: Adverse events	Primary: Combination therapy achieved greater reductions in LDL-C (27.7 vs 16.9%; P≤0.001), TC (17.5 vs 10.3%; P≤0.001), non-HDL-C (23.4 vs 14.0%; P≤0.001) and apo B (17.9 vs 9.8%; P≤0.001) compared to rosuvastatin. Both treatments achieved similar increases in HDL-C (2.1 vs 3.0%; P=0.433) and decreases in TG (11.0 vs 5.3%; P=0.056). A significantly greater proportion of patients receiving combination therapy achieved an LDL-C <100 (73 vs 56%) and <70 mg/dL (25 vs 11%) (P≤0.001 for both). Secondary: There were no between-group differences in the incidences of adverse events or liver transaminase and CK elevations (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
	40 mg)			
Viigimaa et al.[230] (2010) Ezetimibe-simvastatin 10-20 mg/day vs rosuvastatin 10 mg/day	Post hoc analysis Patients 18 to 80 years of age with hypercholesterolemia (LDL-C ≥100 and ≤190 mg/dL) and high cardiovascular risk who were taking a stable dose of none of the following statin medications for ≥6 weeks prior to trial randomization: atorvastatin (10 or 20 mg), fluvastatin (80 mg), pravastatin (40 mg), rosuvastatin (5 mg) or simvastatin (20 or 40 mg)	N=618 6 weeks	Primary: Changes from baseline in lipid parameters stratified by statin potency prior to randomization; proportion of patients achieving LDL-C <100, <77 or <70 mg/dL; non-HDL-C <130 or <100 mg/dL; apo B <90 or <80 mg/dL and LDL-C <100 mg/dL, non-HDL-C <130 mg/dL and apo B <90 mg/dL Secondary: Not reported	Primary: Significant treatment-by-subgroup interaction occurred for LDL-C (P=0.013), TC (P=0.025), non-HDL-C (P=0.032) and apo B (P=0.016) with greater between-treatment differences in favor of combination therapy observed in patients who were previously treated with a high potency statin vs a low potency. Individual and triple target attainment was higher with combination therapy compared to rosuvastatin in patients previously treated with a high or low potency statin (P values not reported). Secondary: Not reported
Catapano et al.[231] (2006) Ezetimibe-simvastatin 10-20, 10-40 or 10-80 mg/day vs	DB, MC, PG, RCT Patients 18 to 81 years of age with LDL-C ≥145 and ≤250 mg/dL; TG ≤350 mg/dL; ALT, AST and CK level <1.5	N=2,959 6 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent changes from baseline in LDL-C at various dose	Primary: At all doses, combination therapy significantly reduced LDL-C compared to rosuvastatin (52 to 61 vs 56 to 57%; P≤0.001). Secondary: Significantly greater reductions in LDL-C with combination therapy were achieved with the 10/20 (P<0.001), 10/40 (P=0.001) and 10/80 mg (P<0.001) compared to rosuvastatin. Combination therapy produced significantly greater reductions in TC

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
rosuvastatin 10, 20 or 40 mg/day	times the upper limit of normal, serum creatinine ≤1.5 mg/dL and HbA_{1c} <9.0% in patients with diabetes		comparisons, HDL-C, TC, apo B, TG, non-HDL-C, LDL-C:HDL-C, TC:HDL-C and hsCRP; proportion of patients who achieved an LDL-C goal <100, <130 or <160 mg/dL; safety	(P<0.001), non-HDL-C (P<0.001), all lipid ratios (P≤0.003), TG (P<0.001) and apo B (P<0.05) compared to rosuvastatin. Increases in HDL-C and decreases in hsCRP were similar between the two treatments (P values not reported). Significantly greater proportions of all patients (P<0.001) and high risk patients (P≤0.005) attained an LDL-C goal <70 mg/dL with combination therapy compared to rosuvastatin across all doses. Safety profiles were comparable between the two treatments. The percent of patients with proteinuria was significantly higher with rosuvastatin compared to combination therapy at doses of 10 vs 10/20 mg (P=0.004) and 40 vs 10/80 mg (P<0.001).
Roeters van Lennep et al.[232] (2008) EASEGO Ezetimibe-simvastatin (EZE/SIMVA) 10-20 mg QD vs doubling of statin dose (atorvastatin 20 mg or simvastatin 40 mg) QD Patients were randomized to continuation of statin monotherapy at a	RCT, OL Patients >18 years of age with controlled stable type 2 diabetes mellitus (>3 months) and/or established coronary heart disease who were on a stable daily statin dose of either atorvastatin 10 mg or simvastatin 20 mg for ≥4 weeks. Entry lipid values while on statin monotherapy were: LDL-C 97 to 193 mg/dL, TG	N=367 15 weeks	Primary: Percentages of patients reaching the ESC goal LDL-C <97 mg/dl Secondary: TC, TG, HDL-C, apo-B, and TC/HDL-C	Primary: Overall, the LDL-C target of <97 mg/dl was achieved in 67% of the patients in the EZE/SIMVA group and 26% of the patients in the doubling statin group. After doubling the simvastatin dose from 20 to 40 mg, 24% of patients achieved LDL-C <97 mg/dl. After switching to EZE/SIMVA, 73% of patients reached LDL-C <97 mg/dl (P<0.0001). After doubling the atorvastatin dose from 10 to 20 mg, 28% of patients achieved LDL-C <97 mg/dl. After switching to EZE/SIMVA, 57% of patients achieved LDL-C 97 mg/dl (P<0.0004). After doubling the statin dose, LDL-C <77 mg/dl was achieved in 3% of patients and in 30% of the patients receiving EZE/SIMVA. Secondary: The mean percent change in TC, TC/HDL-C and apo-B were -6.6%, -6.1% and -7.2%, respectively after doubling the statin dose compared to -17.7%, -13.5%, and -19.7%, respectively in the EZE/SIMVA group (all, P<0.001). HDL-C increased 1.0% after doubling the statin dose compared to -2.6% in the EZE/SIMVA group (P=0.02). There was no significant difference in TG among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
double dose or to EZE/SIMVA	≤354 mg/dL and TC ≤270 mg/dL			There were no significant differences between the treatment groups in adverse events.
Reckless et al.[233] (2008) Ezetimibe-simvastatin (EZE/SIMVA) 10-40 mg QD vs existing statin therapy (with the dose doubled) administered QD	AC, MC, OL, PG, RCT Patients ≥18 years of age hospitalized for an acute coronary event and taking a stable daily dose of one of the following statin medications for ≥6 weeks: atorvastatin (10-40 mg), fluvastatin (20-40 mg), lovastatin (10-20 mg), pravastatin (10-20 mg), rosuvastatin (10-20 mg), or simvastatin (10-40 mg)	N=424 12 weeks	Primary: Absolute LDL-C value at study end point Secondary: TC, TG, HDL-C, non-HDL-C, LDL-C:HDL-C ratio, TC:HDL-C ratio, apo B, CRP, percentages of patients in each treatment group achieving LDL-C ≤100 mg/dL, <77 mg/dL and <70 mg/dL	Primary: Treatment with EZE/SIMVA lowered LDL-C by -25.5 mg/dL (27%) compared to -6.6 mg/dL (4.2%) in the statin group (P≤0.001). The absolute LDL-C value at study end point was 65.7 mg/dL in the EZE/SIMVA group and 85.8 mg/dL in the statin group. Secondary: A greater proportion of patients in the EZE/SIMVA group compared to placebo achieved LDL-C concentrations <100 mg/dL (85.8% vs 72.4%, respectively; P≤0.001), <77 mg/dL (70.1% vs 41.7%, respectively; P≤0.001) and <70 mg/dL (59.8 vs 30.7%, respectively; P≤0.001). Switching to EZE/SIMVA lowered TC by -24.0 mg/dL (14.6%) compared to -5.4 mg/dL (1.7%) in the statin group (P≤0.001). Treatment with EZE/SIMVA produced greater reductions in non- HDL-C (P≤0.001), apo B (P≤0.001), LDL-C/HDL-C (P≤0.001) and TC/HDL-C (P≤0.001) compared to the statin group. Both treatments reduced TG and CRP, and increased HDL-C to a similar extent (P≥0.160 for all). There were no significant differences in adverse events between the two treatment groups.
Fazio et al.[234] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day	DB, MC, RCT Patients 18 to 79 years of age with hyperlipidemia (Types IIa and IIb) with LDL-C 130 to 190 mg/dL, TG ≤500 mg/dL, creatinine <2 mg/dL, creatine kinase ≤2	N=942 64 weeks	Primary: Safety and tolerability of ezetimibe-simvastatin plus niacin ER Secondary: Changes in HDL-C, TG, non-HDL-C and LDL-C	Primary: The most frequent reason for discontinuation was clinical adverse events related to niacin-associated flushing with ezetimibe/simvastatin plus niacin (0.7% for ezetimibe-simvastatin vs 10.3% for ezetimibe/simvastatin plus niacin). A significant number of patients receiving ezetimibe/simvastatin plus niacin discontinued because of low LDL-C levels <50 mg/dL (1.5 vs 7.1%). The overall incidence of clinical adverse events was slightly greater for ezetimibe-simvastatin plus niacin compared to ezetimibe-simvastatin owing to the greater number of patients who experienced drug-related clinical adverse events and drug-related discontinuations with ezetimibe-simvastatin plus niacin, mainly attributed to niacin-associated flushing and pruritis.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs ezetimibe-simvastatin 10-20 mg/day At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.	times the upper limit of normal, transaminases ≤1.5 times the upper limit of normal and HbA_{1c} ≤8%			The percentage of patients with consecutive elevations in ALT or AST of at least three times or greater the upper limit of normal, and creatine kinase of at least ten times or greater the upper limit of normal were low and comparable between treatments. A total of 19 patients had adverse events of increased FPG levels, with eight receiving ezetimibe/simvastatin and 11 receiving ezetimibe-simvastatin plus niacin. Secondary: Ezetimibe-simvastatin plus niacin significantly improved baseline HDL-C, TG, non-HDL-C, LDL-C, apo B, apo AI and Lp ratios compared to ezetimibe-simvastatin at week 64 (P<0.004). The changes in TC were comparable between the two treatment groups and the reduction in hsCRP was numerically greater with ezetimibe-simvastatin plus niacin (P value not reported). Ezetimibe-simvastatin plus niacin increased HDL-C considerably during the first 16 weeks of treatment, and at a lower, but significant, rate from 16 to 24 weeks, and then remained constant throughout 64 weeks. The HDL-C change was significantly greater with ezetimibe-simvastatin plus niacin vs ezetimibe/simvastatin throughout the 64 weeks (P<0.001). The reductions in LDL-C, non-HDL-C and TG observed after four weeks with ezetimibe-simvastatin plus niacin were maintained throughout the 64 weeks. In contrast, the levels remained relatively stable with ezetimibe-simvastatin throughout the 64 weeks (P<0.001) and became significant for non-HDL-C after eight weeks (P=0.002) and LDL-C after 12 weeks (P<0.001).
Fazio et al.[235] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day	Subgroup analysis Hyperlipidemic patients with diabetes mellitus, metabolic syndrome without diabetes mellitus or neither	N=765 at 24 weeks N=574 at 64 weeks	Primary: Changes in HDL-C, TG, non-HDL-C, LDL-C, fasting glucose and uric acid Secondary: Not reported	Primary: The effect of triple therapy on efficacy variables across patient subgroups was generally consistent with the significantly greater improvements observed in the total population compared to niacin and combination therapy. Triple therapy improved levels of LDL-C, other lipids and Lp ratios compared to niacin and combination therapy at 24 and 64 weeks. Triple therapy also increased HDL-C and Lp(a) comparably to niacin and more than combination therapy. Triple therapy also decreased hsCRP more effectively than niacin and comparably to combination therapy. Fasting glucose trended higher for niacin compared to combination therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs ezetimibe-simvastatin 10-20 mg/day At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.				Glucose elevations from baseline to 12 weeks were highest for patients with diabetes (niacin, 24.9 mg/dL; triple therapy, 21.2 mg/dL and combination therapy, 17.5 mg/dL). Fasting glucose levels then declined to pretreatment levels at 64 weeks in all subgroups. New onset diabetes was more frequent among patients with metabolic syndrome than those without for the first 24 weeks and trended higher among those receiving niacin (niacin, 5.1%; combination therapy, 1.7% and triple therapy, 8.8%). Between weeks 24 and 64, five and one additional patient(s) receiving combination (cumulative incidence, 5.9%) and triple therapy (cumulative incidence, 9.2%) were diagnosed with diabetes. Treatment-incident increases in uric acid were higher among patients receiving niacin, but there were no effects on symptomatic gout. Secondary: Not reported
Sharma et al.[236] (2006) Niacin ER-lovastatin 1,500-20 mg/day, combination entity, titrated up to LDL-C goal	MC, OL Patients with HTN and dyslipidemia	N=131 24 weeks	Primary: Percent change from baseline in LDL-C, HDL-C, TG, TC Secondary: Not reported	Primary: Niacin ER-lovastatin therapy was associated with a statistically significant reduction from baseline in LDL-C (38%), TG (21%), and TC (25.2%) at week 24 of therapy (P<0.01). Niacin ER-lovastatin therapy was associated with a statistically significant increase from baseline in HDL-C at week 24 of therapy (18.2%; P<0.01). Secondary: Not reported
Karas et al.[237] (2008) OCEANS <u>Group A:</u> Niacin ER-simvastatin 2,000-20 or 1,000-20 mg/day	AC, MC, OL, PG, Phase III, RCT Patients ≥21 years of age with a diagnosis of primary type II hyperlipidemia or mixed dyslipidemia,	N=641 24 weeks	Primary: Group A: mean percent change in non-HDL-C Group B: non-inferiority of niacin ER/simvastatin 2,000/40 mg to	Primary: In Group A, the mean percent changes in non-HDL-C at 24 weeks were significantly greater with niacin ER/simvastatin 1,000/20 and 2,000/20 mg than with simvastatin 20 mg (-13.6 and -19.5 vs -5.0%, respectively; P<0.05). In Group B, the mean percent change in non-HDL-C at 24 weeks with niacin ER/simvastatin 2,000/40 mg was non-inferior to that of simvastatin 80 mg (-7.6 vs -6.0%; 95% CI, -7.7 to 4.5). Similar results were obtained in non-inferiority comparisons between niacin ER/simvastatin 1,000/40 mg and simvastatin 80 mg (-6.7 vs -6.0%; 95% CI, -6.6 to 5.3).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs simvastatin 20 mg/day Group B: Niacin ER-simvastatin 1,000-40 or 2,000-40 mg/day vs simvastatin 80 mg/day All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing. All patients were instructed to take aspirin or ibuprofen to minimize flushing.	proof of reasonable compliance with a standard cholesterol lowering diet for 4 weeks before screening and for the duration of the trial, and LDL and/or non-HDL levels above normal		simvastatin 80 mg in mean percent change in non-HDL Secondary: Mean percent change in LDL-C, TG and HDL-C	Secondary: In Group A, the mean percent change in LDL-C at 24 weeks with niacin ER/simvastatin 1,000/20 and 2,000/20 mg were non-superior to simvastatin 20 mg (-11.9 and -14.3 vs -6.7%, respectively) (P value not provided). However, mean percent reduction in TG and mean percent increase in HDL-C with niacin ER/simvastatin 1,000/20 and 2,000/20 mg were “superior” to simvastatin 20 mg (TG, -26.5 and -38 vs -15.3%, respectively, HDL, 20.7 and 29% vs 7.8%, respectively) (P values not provided).
Ballantyne et al.[238] (2008) SEACOAST I Niacin ER-simvastatin 1,000-	AC, DB, MC, RCT High risk patients with primary or mixed dyslipidemia	N=319 24 weeks	Primary: Percentage change from baseline in non-HDL-C Secondary:	Primary: Combination therapy achieved significant improvements in non-HDL-C. Median change from baseline at week 24 in non-HDL-C was -13.9, -22.5 ($P<0.01$) and -7.4% ($P<0.001$) for niacin ER-simvastatin 1,000-20 mg/day, niacin ER-simvastatin 2,000-20 mg/day and simvastatin. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
20 or 2,000-20 mg/day vs simvastatin 20 mg/day All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing.			Percent change from baseline in LDL-C, HDL-C, TC/HDL-C, TG, apo B and apo AI	Combination therapy was associated with nonsignificant additional decreases in LDL-C compared to simvastatin. Both combination therapy regimens had significantly greater decreases in TG, Lp(a), apo B and TC:HDL-C (P values not reported). Combination therapy also achieved significant increases in HDL-C and apo AI/apo B.
Ballantyne et al.[239] (2008) SEACOAST II Niacin ER-simvastatin (NER/S) 2,000-40 mg QD vs niacin ER-simvastatin (NER/S) 1,000-40 mg QD vs simvastatin 20 mg/day	AC, DB, MC, RCT Men and women ≥21 years of age, compliant with standard cholesterol-lowering diet for ≥4 weeks prior to screening; non-HDL cholesterol ≥130 mg/dL (CHD or CHD risk equivalent), ≥160 mg/dL (≥2 risk factors), ≥190 mg/dL (0 to 1 risk factors)	N=343 24 weeks	Primary: Percent change from baseline to week 24 in non-HDL-C Secondary: Percent change from baseline to week 24 in LDL-C, HDL-C, TC:HDL-C ratio, TG, Lp(a), apoB, and apoAI	Primary: Percent changes from baseline to week 24 in non-HDL-C in both NER/S groups were non-inferior to the simvastatin 80 mg/day group. Median changes in non-HDL-C were -10.1% for simvastatin 80 mg, -11.3% for NER/S 1,000-40 mg, and -17.1% for NER/S 2,000-40 mg. Secondary: Both NER/S treatment groups significantly reduced TG, Lp(a), and TC:HDL-C ratio, and significantly increased HDL-C and apoAI levels compared to patients receiving simvastatin 80 mg (P<0.01 and P<0.001). No significant differences in LDL-C or apoB were noted between the three treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
All simvastatin monotherapy patients received niacin IR 50 mg/day to prevent unblinding due to flushing.				
Charland et al.[240] (2010) High potency dyslipidemia pharmacotherapy (niacin ER-lovastatin, niacin ER-simvastatin, rosuvastatin and ezetimibe/simvastatin	MA (120 unique reports) Patients with hyperlipidemia	N=43,974 Duration varied (≥4 weeks)	Primary: Percent change from baseline in lipid parameters, cardiovascular events Secondary: Not reported	Primary: All of the high potency therapies lowered LDL-C by ≥45%, with the higher doses of ezetimibe/simvastatin and rosuvastatin achieving the greatest LDL-C reduction of -60 and -54%, respectively. In general, percent lipid changes for ezetimibe/simvastatin and rosuvastatin increased in a significant dose dependent manner for TC and LDL-C. With niacin-containing therapies, percent changes in these parameters were flat, and no significant differences between moderate and high doses were observed. Ezetimibe/simvastatin and rosuvastatin did not demonstrate a significant difference in percent change in HDL-C throughout the doses evaluated. Non-niacin-containing therapies appeared to have a flat dose response curve, with weighted percent HDL-C changes between 5 and 9%. Niacin-containing therapies achieved a significant dose response effect. There was no significant difference in percent change in TG with any dose for ezetimibe/simvastatin or rosuvastatin (5, 20 and 40 mg/day). Niacin-containing therapies also demonstrated greater weighted percent changes in TG lowering (-40%) compared to ezetimibe/simvastatin or rosuvastatin (-31 and -24%). In evaluating percent changes in TC between the therapies there was no significant difference between rosuvastatin 40 mg, ezetimibe/simvastatin 10/80 mg and niacin ER/simvastatin. For LDL-C, there were significant differences between many of the therapies at various doses of rosuvastatin, ezetimibe/simvastatin, niacin ER/lovastatin and niacin ER/simvastatin; however, there was no significant difference in percent change in LDL-C between rosuvastatin 40 mg, ezetimibe/simvastatin 10/40 or 10/80 mg or niacin ER/simvastatin 2,000/40 mg.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				All of the high-potency therapies are predicted to reduce cardiovascular event rates by >50%, except for the lowest dose of ezetimibe/simvastatin (10/10 mg) and niacin ER/lovastatin (500/20 mg). There was no significant difference in predicted event risk reduction between the largest dose of niacin ER/lovastatin (2,000/40 mg) and niacin ER/simvastatin (2,000/40 mg); however, there was a significant difference in predicted event reduction between either of the highest doses of niacin ER/lovastatin (2,000/40 mg) and niacin ER/simvastatin (2,000/40 mg) compared to all of the doses of rosuvastatin or ezetimibe/simvastatin. The average percent cardiovascular event reduction for ezetimibe/simvastatin, rosuvastatin, niacin ER/lovastatin and niacin ER/simvastatin was 60, 58, 61 and 72%, respectively. Secondary: Not reported
Adverse Events				
Newman et al.[241] (2006) Atorvastatin 10 or 80 mg QD vs placebo	MA (42 trials) Patients with various cardiovascular risks, LDL-C ≥130 mg/dL and TG ≤600 mg/dL	N=14,236 2 weeks to 52 months	Primary: Adverse effects Secondary: Not reported	Primary: Treatment-related side effects were similar between treatments (P value not reported). Treatment-associated myalgia was observed in 1.4, 1.5 and 0.7% of patients receiving atorvastatin 10 mg, 80 mg and placebo, respectively (P value not reported). No cases of rhabdomyolysis were reported with atorvastatin or placebo (P value not reported). Elevations in hepatic transaminases at least three times the upper limit of normal were observed in 0.1, 0.6 and 0.2% of patients receiving atorvastatin 10 mg, 80 mg and placebo, respectively (P value not reported). Secondary: Not reported
Shepherd et al.[242] (2003) Rosuvastatin 5 to 40 mg QD	MA (33 RCTs) Patients with dyslipidemia	N=16,876 25,670 patient-years	Primary: Adverse events, elevation in transaminases, CK, myopathy, dipstick-	Primary: The incidence of adverse events was similar with rosuvastatin and placebo (52.1 vs 51.8%, respectively; P value not reported). The incidence of adverse events was similar across all the active treatments (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
vs atorvastatin 10 to 80 mg QD vs simvastatin 10 to 80 mg QD vs pravastatin 10 to 40 mg QD vs placebo			positive proteinuria, estimated glomerular rate Secondary: Not reported	The incidence of elevation in transaminases and CK, myopathy, dipstick-positive proteinuria and estimated glomerular rate was similar across all the active treatment groups (P value not reported). Secondary: Not reported
Silva et al.[243] (2006) Statins (atorvastatin, pravastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin) vs placebo	MA (18 PRO, RCTs) Patients receiving statin therapy or placebo	N=71,108 Up to 317 weeks	Primary: Adverse events, cardiovascular events Secondary: Not reported	Primary: Statin therapy significantly increased the risk of any adverse events by 39% compared to placebo (OR, 1.4; 95% CI, 1.09 to 1.80; P=0.008). Consequently, out of 197 statin-treated patients, one patient would experience an adverse event (95% CI, 24 to 37; P value not reported). Statin therapy was associated with a significant 26% reduction in the risk of a clinical cardiovascular event compared to placebo (OR, 0.74; 95% CI, 0.69 to 0.80; P<0.001). Consequently, the NNT to prevent one additional cardiovascular event was 27. Rosuvastatin trials were not included in the analysis of cardiovascular risk reduction due to inadequate data. The incidence of adverse effects during statin administration was observed in the following order, from highest to lowest: atorvastatin >pravastatin=simvastatin=lovastatin>fluvastatin. Secondary: Not reported
Kashani et al.[244]	MA (35 DB,	N=74,102	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
(2006) Statins (atorvastatin 20 to 80 mg/day, fluvastatin 2.5 to 80 mg/day, lovastatin 10 to 80 mg/day, pravastatin 10 to 160 mg/day, rosuvastatin 1 to 80 mg/day, simvastatin 2.5 to 80 mg/day) vs placebo	RCTs) Patients ≥18 years of age with hyperlipidemia	 Up to 65 months	Adverse events (myalgia, CK elevation, rhabdo-myolysis, transaminase elevation), discontinuation due to adverse event Secondary: Not reported	Statin therapy was associated with a nonsignificant increase in the risk of myalgias (risk difference, 2.7; 95% CI, -3.2 to 8.7; P=0.37), CK elevation (risk difference, 0.2; 95% CI, -0.6 to 0.9; P=0.64), rhabdomyolysis (risk difference, 0.4; 95% CI, -0.1 to 0.9; P=0.13) or discontinuation due to adverse events (risk difference, -0.5; 95% CI, -4.3 to 3.3; P=0.80) compared to placebo. Statin therapy was associated with a significant risk of transaminase elevations (risk difference, 4.2; 95% CI, 1.5 to 6.9; P<0.01) compared to placebo. When individual statins were compared to placebo, atorvastatin was the only statin with a significant increase in the risk of myalgias (P=0.04). When individual statins were compared to placebo, fluvastatin (P<0.01) and lovastatin (P=0.05) were the only statins with a significant increase in the risk of transaminase elevations. Secondary: Not reported
McClure et al.[245] (2007) Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin), stratified by ≤40 mg and >40 mg/day lovastatin equivalent dose vs placebo	MA (119 DB, RCTs) Patients ≥18 years of age with hyperlipidemia	N=86,000 Up to 65 months	Primary: Adverse events (myalgia, myositis, rhabdo-myolysis), discontinuations due to adverse events Secondary: Not reported	Primary: Statin therapy was associated with a nonsignificant increase in the risk of myalgias (OR, 1.09; 95% CI, 0.97 to 1.23; P=0.471), rhabdomyolysis (OR, 1.59; 95% CI, 0.54 to 4.70; P=0.544) or myositis (OR, 2.56; 95% CI, 1.12 to 5.85; P=0.987) compared to placebo. Statin therapy was associated with a significantly lower incidence of discontinuations due to adverse events (OR, 0.88; 95% CI, 0.84 to 0.93; P<0.001) compared to placebo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Law et al.[246] (2006) Statins (lovastatin, atorvastatin, pravastatin, simvastatin, fluvastatin) vs placebo	SR (2 cohort studies and 21 PC, RCTs) Patients receiving statin therapy or placebo	N=not reported Up to 6.1 years	Primary: Incidence of rhabdomyolysis, myopathy, renal failure, elevated ALT, renal failure, proteinuria and peripheral neuropathy Secondary: Not reported	Primary: The incidence of rhabdomyolysis associated with the use of statins in two cohort and RCTs was 3.4 (95% CI, 1.6 to 6.5) per 100,000 patient-years (P value not reported). The incidence of rhabdomyolysis associated with the use of statins in addition to gemfibrozil in two cohort studies was 35 (95% CI, 1 to 194) per 100,000 patient-years (P value not reported). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately four times higher in patients receiving lovastatin, simvastatin or atorvastatin compared to those receiving fluvastatin or pravastatin (P<0.001). The notification of rhabdomyolysis to the FDA adverse events reporting system was approximately 15 times higher in patients receiving statins in combination with gemfibrozil (21 per 100,000 patient-years; 95% CI, 17 to 25) compared to those receiving statin therapy (0.70 per 100,000 patient-years; 95% CI, 0.62 to 0.79; P<0.001). The incidence of myopathy associated with the statin therapy in RCTs was five (95% CI, -17 to 27) per 100,000 patient-years (P value not reported). The incidence of liver failure associated with statin therapy, reported to the FDA adverse events reporting system, was 0.1 per 100,000 patient-years of use (P value not reported). Statin therapy in patients with elevated ALT would lead to liver disease in less than one person (P value not reported). Statin therapy was not associated with a higher incidence of renal failure or proteinuria compared to placebo (P value not reported). Patients receiving statin therapy have 1.8 odds of experiencing peripheral neuropathy compared to placebo (95% CI, 1.1 to 3.0; P<0.001). Secondary: Not reported
Dale et al.[247] (2007)	MA (9 RCTs) Patients receiving	N=21,765 Up to 5 years	Primary: Incidence of elevations in	Primary: Intensive statin therapy was associated with a significant increased risk of AST or ALT elevation compared to the moderate statin therapy (1.5 vs 0.4%; RR,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
Intensive statin therapy; hydrophilic (atorvastatin 80 mg/day) and lipophilic statins (simvastatin 40 to 80 mg/day, lovastatin 76 mg/day) vs moderate statin therapy; hydrophilic (atorvastatin 10 mg/day, pravastatin 40 mg/day) and lipophilic statins (simvastatin 20 to 40 mg/day, lovastatin 4 mg/day)	statin therapy		AST, ALT or CK Secondary: Not reported	3.10; 95% CI, 1.72 to 5.58; P=0.002). Intensive statin therapy was associated with a nonsignificant risk of CK elevation compared to the moderate statin therapy (0.10 vs 0.02%; RR, 2.63; 95% CI, 0.88 to 7.85; P=0.89). In a subanalysis of hydrophilic and lipophilic statins, while no cases of CK elevation occurred in the hydrophilic intensive statin group, patients on lipophilic intensive statin therapy experienced a nonsignificant risk in CK elevation (RR, 6.09; 95% CI, 1.36 to 27.35; P≥0.11). Secondary: Not reported
Silva et al.[248] (2007) Intensive statin therapy (atorvastatin 80 mg/day, simvastatin 80 mg/day) vs	MA (4 RCTs) Patients with ACS or stable CAD receiving statins for the reduction of secondary cardiovascular events	N=27,548 3.4 years	Primary: CK ≥10 times the upper limit of normal, with or without myalgia; ALT or AST ≥3 times the upper limit of normal; rhabdo-myolysis; drug-induced adverse	Primary: Intensive statin therapy was associated with a significant increased risk of any adverse event compared to moderate statin therapy (OR, 1.44; 95% CI, 1.33 to 1.55; P<0.001). Consequently, out of 30 patients treated with intensive statin therapy, one patient would experience an adverse event (95% CI, 24 to 37; P value not reported). Intensive statin therapy was associated with a significant increased risk (absolute risk, 2.14%) of an adverse drug event requiring discontinuation of drug therapy (OR, 1.28; 95% CI, 1.18 to 1.39; P≤0.001). Intensive statin therapy was associated with a significant increased risk

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
moderate statin therapy (atorvastatin 10 mg/day, simvastatin 20 mg/day, pravastatin 40 mg/day)			effects requiring drug discontinuation; any drug-induced adverse event; all-cause mortality; cardiovascular death; nonfatal MI; and stroke Secondary: Not reported	(absolute risk, 1.2%) of an elevation in AST and ALT at least three times the upper limit of normal (OR, 4.84; 95% CI, 3.27 to 6.16; P≤0.001). Consequently, out of 86 patients treated with intensive statin therapy, one patient would experience an elevation in AST and ALT at least three times the upper limit of normal (95% CI, 72 to 106; P value not reported). Intensive statin therapy was associated with a significant increased risk (absolute risk, 0.07%) of an elevation in CK ≥10 times the upper limit of normal (OR, 9.97; 95% CI, 1.28 to 77.92; P=0.028). Consequently, out of 1,534 patients treated with intensive statin therapy, one patient would experience an elevation in CK ≥10 times the upper limit of normal (P value not reported). There was no difference in the incidence of rhabdomyolysis between the treatments (P value not reported). Intensive statin therapy was associated with a nonsignificant reduction in all-cause mortality compared to moderate-dose statin therapy (P=0.185). Intensive statin therapy was associated with a significant reduction in the risk for cardiovascular death (P=0.031), nonfatal MI (P<0.001) and stroke (P=0.004). Consequently, the NNT to prevent one additional cardiovascular death, MI or stroke was 229, 99 and 166, respectively. Secondary: Not reported
Strony et al.[249] (2008) Ezetimibe 10 mg QD coadministered with either pravastatin 10 to 40 mg QD or simvastatin 10 to 80 mg QD	Pooled analysis of 2 ES, MC, OL Patients with primary hypercholesterolemia	N=795 12 to 15 months	Primary: Tolerability Secondary: LDL-C, HDL-C, TG, TC, and proportion of patients achieving LDL-C goal	Primary: Treatment-emergent adverse events were reported in 81% of patients receiving ezetimibe plus pravastatin (15 months) and in 84% of patients receiving ezetimibe plus simvastatin (12 months). The most commonly reported treatment-emergent adverse events were upper respiratory tract infection (18%), headache (11%), musculoskeletal pain (10%), arthralgia (10%), sinusitis (10%), abdominal pain (8%), bronchitis (6%), coughing (6%), nausea (6%), back pain (5%), myalgia (5%), chest pain (5%), and fatigue (5%) with ezetimibe plus pravastatin. The most commonly reported treatment-emergent adverse events were upper

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	Endpoints	Results
				respiratory tract infection (19%), arthralgia (11 %), musculoskeletal pain (10%), headache (9%), back pain (8%), myalgia (8%), abdominal pain (7%), nausea (7%), pharyngitis (6%), coughing (5%), fatigue (5%), and urinary tract infection (19%) with ezetimibe plus simvastatin. During the ezetimibe plus pravastatin extension study, 7% experienced serious adverse events. During the ezetimibe plus simvastatin extension study, serious adverse events were reported in 10% of patients. Life-threatening adverse events were reported in four patients in the ezetimibe plus simvastatin study. The incidence of newly reported adverse events did not increase over time in either study. In the ezetimibe plus pravastatin study, 1% of patients experienced increases in ALT/AST >3 X upper limit or normal, whereas this was not reported in the patients receiving ezetimibe plus simvastatin. Secondary: The mean LDL-C was reduced by 36.5 and 40.4% in the ezetimibe plus pravastatin and ezetimibe plus simvastatin studies, respectively. Similar reductions in TC and TG, and an increase in HDL-C, were achieved and maintained throughout the study period in both studies. In the ezetimibe plus pravastatin study, 85% of patients achieved their NCEP ATP III LDL-C goal and 80% of patients in the ezetimibe plus simvastatin study achieved their recommended goal.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate-release, QD=once daily, SR=sustained-release, TID=three times daily; XL=extended-release, XR=extended-release
Study abbreviations: AC=active comparator, DB=double blind, DD=double dummy, ES=extension study, FU=follow-up, MA=meta-analysis, MC=multicenter, NI=noninferiority, OL=open label, PA=parallel-arm, PC=placebo-controlled, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, XO=cross-over
Miscellaneous abbreviations: ACS=acute coronary syndrome, ALT=alanine aminotransferase, apo=apolipoprotein, ARR=absolute risk reduction, AST=aspartate aminotransferase, BMI=body mass index, BNP=B-type natriuretic peptide, BP=blood pressure, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, CIMT=carotid intima-media thickness, CK=creatine kinase, CKD=chronic kidney disease, CPK=creatinine phosphokinase, CRP=C-reactive protein, DBP=diastolic blood pressure, ECG=electrocardiogram, eGFR=estimated glomerular filtration rate, FBG=fasting blood glucose, FH=familial hypercholesterolemia, GFR=glomerular filtration rate, HAART=highly active anti-retroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, heFH=heterozygous familial hypercholesterolemia, HIV=human immunodeficiency

virus, hoFH=homozygous familial hypercholesterolemia, HOMA=homeostasis model assessment, HR=hazard ratio, hsCRP=high-sensitivity C-reactive protein, HTN=hypertension, IMT=intima-medial thickness, IDL-C=intermediate-density lipoprotein cholesterol, JNC 7=Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program, Adult Treatment Panel, NNT=number needed to treat, NYHA=New York Heart Association, OR=odds ratio, PAD=peripheral arterial disease, PAV=percent atheroma volume, PCI=percutaneous coronary intervention, RR=relative risk, SBP=systolic blood pressure, SE=standard error, STEMI=ST-segment myocardial infarction, TAV=total atheroma volume, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TRL=triglyceride lipoprotein, VLDL-C=very low-density lipoprotein, VTE=venous thromboembolism

Additional Evidence

Dose Simplification

Wongwiwatthananukit et al evaluated the safety and efficacy with rosuvastatin 10 mg administered once-daily compared to every-other-day in patients with primary hypercholesterolemia. There was a significantly larger reduction in low-density lipoprotein cholesterol (LDL-C) with once daily therapy compared to every-other-day administration (48 vs 39%, respectively; P=0.011). Total cholesterol and triglycerides were significantly lower with once daily therapy (P<0.05). However, there was no difference in the percentage of patients achieving their National Cholesterol and Education Program Adult Treatment Panel III LDL-C goals (P=0.18).[250]

LaFleur et al evaluated the differences in adherence and persistence with (1) a fixed-dose combination product containing lovastatin and extended-release niacin, (2) statin monotherapy, (3) extended-release niacin monotherapy, and (4) extended-release niacin taken with lovastatin as separate formulations. A total of 2,389 patients met the eligibility criteria and were followed for one year. All groups exhibited an adherence rate >80%. Patients receiving extended-release niacin and lovastatin taken separately demonstrated higher adherence rates compared to those on the fixed-dose product (90 vs 88%; P=0.033). In addition, patients were less adherent to statin monotherapy than to either the fixed-dose combination product or niacin monotherapy (81, 90, and 89%, respectively; P<0.05). At 12 months, all treatment groups had a persistence rate of <20%. At nine months, patients randomized to niacin monotherapy exhibited a significantly lower rate of persistence compared to the rest of the groups (P<0.05). Since this was an adherence study only, based on an evaluation of pharmacy claims, the study did not measure the impact of adherence on LDL-C or other cholesterol goals.[251]

Balu et al retrospectively evaluated medication adherences rates in patients treated with the fixed-dose combination of niacin extended-release and lovastatin (NERL) compared to the multi-pill combination of niacin extended-release plus lovastatin (NER/L) or simvastatin (NER/S) using an integrated managed care database. Adherence rates were greater among patients initiating therapy with NERL compared to NER/S or NER/L P<0.0001). A higher percentage of patients initiating therapy with NERL (34.2%) exhibited optimal adherence (>80%) compared to those initiating therapy with NER/S (29.6%; P<0.0001) or NER/L (25.9%; P<0.0001). There were fewer cardiovascular disease-associated emergency room visits in patients with optimal adherence initiating therapy with NERL compared to those with optimal adherence initiating therapy with NER/S or NER/L (P=0.003), inpatient visits (P=0.018, outpatient visits (P<0.0001), and prescription fills (P<0.0001). Patients with optimal adherence had an 8% decrease (P=0.023) in annual cardiovascular disease-attributable total medical resource utilization compared to patients with suboptimal adherence (<80%).[252]

Patel et al evaluated adherence rates in patients newly initiated on dual therapy with a calcium channel blocker and a statin (as either a fixed-dose combination product or administration of each component separately). In this six month, retrospective, pharmacy claims database analysis, the authors found that the percentage of patients achieving adherence rates ≥80% were: 67.7% with amlodipine-atorvastatin; 49.9% with amlodipine plus atorvastatin; 40.4% with amlodipine plus other statins; 46.9% with other calcium channel blockers plus atorvastatin; 37.4% with other calcium channel blocker plus other statin (P<0.0001 amlodipine-atorvastatin vs all other cohorts).[253]

Stable Therapy

Cheetham et al evaluated the efficacy and safety of switching patients from Zocor® to generic lovastatin. Patients switching to lovastatin experienced a reduction in LDL-C, an increase in high-density lipoprotein cholesterol and a decrease in triglycerides. Rates of alanine aminotransferase and creatine kinase elevations were not found to be significantly different before or after conversion.[254]

Usher-Smith et al examined the effects of switching patients from atorvastatin to simvastatin in a two year retrospective analysis. Patients initially receiving atorvastatin 10 and 20 mg were converted to simvastatin 10, 20, or 40 mg, respectively. The change in therapy was not associated with a significant alteration in baseline total cholesterol levels (P=0.06).[255]

Impact on Physician Visits

A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the HMG-CoA Reductase Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Atorvastatin	tablet	Lipitor®*	$$$-$$$$	$
Fluvastatin	capsule, extended-release tablet	Lescol®*, Lescol XL®	$$$$	$$$$
Lovastatin	extended-release tablet, tablet	Altoprev®, Mevacor®*	$$$$$	$
Pitavastatin	tablet	Livalo®	$$$$	N/A
Pravastatin	tablet	Pravachol®*	$$$-$$$$	$
Rosuvastatin	tablet	Crestor®	$$$$	N/A
Simvastatin	tablet	Zocor®*	$$$$	$
Combination Products				
Amlodipine and atorvastatin	tablet	Caduet®*	$$$$-$$$$$	$$$$
Ezetimibe and simvastatin	tablet	Vytorin®	$$$$	N/A
Niacin and lovastatin	extended-release tablet	Advicor®	$$$$	N/A
Niacin and simvastatin	extended-release tablet	Simcor®	$$$-$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The HMG-CoA reductase inhibitors (statins) are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia (refer to Table 4 for specific indications). The fixed-dose combination products (amlodipine and atorvastatin, ezetimibe and simvastatin, niacin and lovastatin, and niacin and simvastatin) are indicated for use when dual therapy is appropriate.[1-12] Statins can decrease low-density lipoprotein cholesterol (LDL-C) by 18 to 60% and triglycerides (TG) by 7% to 30%, as well as increase high-density lipoprotein cholesterol (HDL-C) by 5% to 15% when administered as monotherapy.[14,15] Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and fixed-dose amlodipine and atorvastatin are available in a generic formulation.

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease (CHD) or coronary heart disease equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant, niacin, or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy. Choice of statin and dose should be based on cost and the amount of lipid lowering required for a specific patient. Patients with risk factors for CHD but no history of disease are likely to decrease their risk of CHD with lipid lowering therapy. [13] Guidelines do not give preference to statin over another [14,15,17-21]

Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, total cholesterol, and TG, as well as positively impact other lipid/lipoprotein parameters. Studies have also demonstrated that aggressive lipid-lowering with a statin allows patients to reach their National Cholesterol and Education Program Adult Treatment Panel III LDL-C goals. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens.[23-122,211-240] The statins differ in their potency and their effects on LDL-C are dose-dependent. Atorvastatin and rosuvastatin are the most potent agents available and can lower LDL-C by ~60%. However, most patients will likely not require this level of LDL-C reduction to achieve their individual goals of therapy.[13,16] In general, the combination products do not offer any significant clinical advantage over coadministration of their individual components.

All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, while the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke.[1-12,123-210] Atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin have been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention). In addition, fluvastatin, lovastatin, pravastatin, and rosuvastatin have been shown to slow progression of coronary atherosclerosis in patients with CHD. No incremental benefit of the combination statin products on cardiovascular morbidity and mortality has been established over and above that demonstrated for the single entity statin products.[1-12]

The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by one to two percent of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatine kinase. Pravastatin and rosuvastatin do not undergo extensive first-pass metabolism; therefore, they are associated with a lower risk for drug interactions. Atorvastatin, lovastatin, and simvastatin are primarily metabolized by the cytochrome P450 (CYP) 3A4 isoenzyme, while fluvastatin is metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles.[13,16]

There is insufficient evidence to support that one brand HMG-CoA reductase inhibitor is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand HMG-CoA reductase inhibitors within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand HMG-CoA reductase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antilipemic Agents, Miscellaneous
AHFS Class 240692
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I. Overview

The antilipemic agents are categorized into five different American Hospital Formulary Service (AHFS) classes, including bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, HMG-CoA reductase inhibitors (statins), and miscellaneous antilipemic agents. The agents which make up these classes differ with regards to their Food and Drug Administration (FDA)-approved indications, mechanism of action, efficacy, safety profiles, tolerability, and ease of use.

Niacin and omega-3 acid ethyl esters are the only miscellaneous antilipemic agents that are included in this review. Niacin favorably affects all lipids and lipoproteins when given in pharmacological doses; however, the mechanism of action is not completely understood.[1,2] Niacin has several effects on lipid metabolism including inhibition of hepatic production of very low-density lipoprotein cholesterol (VLDL-C), and consequently its metabolite low-density lipoprotein cholesterol (LDL-C). In addition, it decreases plasma concentrations of triglycerides (TGs) (20 to 50%), very low-density lipoprotein remnants, and intermediate density lipoprotein. Administration of niacin also causes a shift in low-density lipoprotein composition from small, dense particles to larger, more buoyant particles. Lastly, niacin increases high density lipoprotein cholesterol (HDL-C) (15 to 35%) both by reducing lipid transfer of cholesterol from HDL-C to VLDL-C, and by delaying HDL-C clearance. Niacin can decrease LDL-C by 5 to 25%.[1,3]

Modifications in lipids can also be effected by a number of dietary approaches or specific dietary supplements. Like medication classes, these modalities also differ with respect to their mechanism of action and to the degree and type of lipid modification.[4] Rich sources of omega-3-fatty acids come from fatty fish and plant sources, and fish oil as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). When administered at high doses they can reduce levels of TGs by approximately 50%.[1,4,5] The mechanism by which this occurs is thought to be caused by the inhibition of VLDL-C.[4] In general, omega-3-fatty acids have no effect on LDL-C, but large doses have been shown to reciprocally increase LDL-C levels in patients with hypertriglyceridemia.[1] More recent clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease.[1,6,7] Lovaza® is the only FDA-approved prescription omega-3 fatty acid product that is currently available for the treatment of hypertriglyceridemia. Each 1 g capsule contains at least 900 mg of ethyl esters of omega-3 fatty acids sourced from fish oil, which are predominantly EPA (approximately 465 mg) and DHA (approximately 375 mg).[8] The total EPA and DHA dose recommended for TG-lowering is approximately 2 to 4 g per dasy.[9]

There are over-the-counter (OTC) niacin products that are currently available, and these products are labeled as dietary supplements. While these supplements are "generally recognized as safe", the FDA does not examine the efficacy and safety of these products or regulate the manufacturing process.[9,10] The FDA has imposed statutory restrictions prohibiting manufacturers of dietary supplements from claiming that their products "treat, cure, or prevent any disease". Without FDA regulation, the content of nicotinic acid in niacin products is not guaranteed.[9] The American Heart Association states that "dietary supplement niacin must not be used as a substitute for prescription niacin" and "it should not be used for lowering cholesterol because of the potential for very serious side effects".[11]

The miscellaneous antilipemic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Niacin is available OTC in a generic formulation. This class was last reviewed in August 2010.

Table 1. Antilipemic Agents, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Niacin	extended-release capsule*, extended-release tablet*, tablet*	Niacor®, Niaspan®	Niacor®, niacin
Omega-3 acid ethyl esters	capsule	Lovaza®	none

*Product is also available over-the-counter.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antilipemic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antilipemic Agents, Miscellaneous

Clinical Guideline	Recommendation
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines[12] (2004)**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid).

Clinical Guideline	Recommendation
	Treatment of homozygous familial hypercholesterolemia • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). Treatment of familial defective apolipoprotein B-100 • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. Treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report[1] (2002)**	General recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver

Clinical Guideline	Recommendation
	disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. Omega-3 fatty acids • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update[6] (2011)**	Lipid management • Goal: treatment with statin therapy; use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70 mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable. • Lifestyle modifications (daily physical activity and weight management) are strongly recommended for all patients. • In addition to lifestyle modifications, statin therapy should be prescribed in the absence of contraindications or documented adverse events. • An adequate dose of statin should be used that reduces LDL-C to <100 mg/dL and achieves ≥30% lowering of LDL-C. • Patients who have TG ≥200 mg/dL should be treated with statins to lower non-HDL-C to <130 mg/dL. • Patients who have TG >500 mg/dL should be started on fibrate therapy in addition to statin therapy to prevent acute pancreatitis. • If treatment with a statin does not achieve the goal selected for an individual patient, intensification of LDL-C-lowering drug therapy with a bile acid sequestrant or niacin is reasonable.

Clinical Guideline	Recommendation
	• For patients who do not tolerate statins, LDL-C-lowering therapy with bile acid sequestrants and/or niacin is reasonable. • It is reasonable to treat very high risk patients with statin therapy to lower LDL-C to <70 mg/dL. • In patients who are at very high risk and who have TG ≥200 mg/dL, a non-HDL-C goal of <100 mg/dL is reasonable. • The use of ezetimibe may be considered for patients who do not tolerate or achieve target LDL-C with statins, bile acid sequestrants, and/or niacin. • For patients who continue to have an elevated non-HDL-C while on adequate statin therapy, niacin or fibrate therapy or fish oil may be reasonable. • For all patients, it may be reasonable to recommend omega-3 fatty acids from fist or fish oil capsules (1 g/day) for cardiovascular disease risk reduction.
Institute for Clinical Systems Improvement: **Lipid Management in Adults[7] (2011)**	<u>Clinical highlights</u> • Initiate a statin with patients who have a history of CHD or CHD risk equivalents. • Establish lipid goals based on risk level. • Instruct patients on healthy lifestyle and adjunctive measures. • Patient adherence with recommended therapy should be reinforced during scheduled follow-up. • An LDL goal <70 mg/dL can be considered for patients with established coronary artery disease, non-cardiac atherosclerosis, or coronary artery disease equivalent. <u>Ongoing drug therapy</u> • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Combination therapy can be considered on an individual basis. • No primary prevention trials have addressed pharmacologic lipid treatment in patients at low risk for CHD, and there is no evidence to support drug treatment in this population. • Primary prevention trials of pharmacologic lipid-lowering have not shown a decrease in mortality, although most have shown about a 30% reduction in CHD events. <u>Monotherapy</u> • Patients with risk factors for CHD but no history of disease who receive lipid-lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy, and trials have consistently shown a decrease in risk of death from CHD. • The use of statin therapy is recommended in patients with established CHD or CHD risk equivalents (includes occlusive carotid disease, peripheral vascular disease, abdominal aortic aneurysm, and diabetes). • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment with statins should be pursued. Statins also have a modest effect on reducing TG and increasing HDL-C. • Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • If a patient is intolerant to a statin, patients should try another statin before ruling all of them out. • Incidence of muscle symptoms or signs is the most prevalent and

Clinical Guideline	Recommendation

	important adverse effect of statin therapy.
	• Specific statin and dose should be selected based on cost and amount of lipid-lowering required.
	• If patients are unable to take a statin, then bile acid sequestrants, niacin, fibric acid derivatives or fibrates, and ezetimibe are available.
	• Many crystalline (immediate-release) and sustained-release preparations of niacin are available over-the-counter. The extended-release preparation of niacin is a prescription drug. Niacin exerts favorable effects on all lipids and lipoproteins, and is good for mixed hyperlipidemia.
	• Long-term use of niacin is usually limited for many patients due to side effects (e.g., flushing and pruritus, liver toxicity, gastrointestinal complaints, etc).
	• Combination therapy with niacin and a statin may increase the risk of myopathy based on early experience with lovastatin.
	• Prior to initiating a fibric acid (gemfibrozil, fenofibrate, and fenofibrate micronized), lifestyle therapies should be intensified for moderately elevated TG. With fibric acids, TG are reduced 30 to 50%, HDL-C is increased 10 to 20%, TC is reduced 5 to 20% in patients without elevated TG, and the effect on LDL-C is variable. Fibric acids are good for severe hypertriglyceridemia (>500 mg/dL) in patients at risk for pancreatitis and for prevention of CHD (not proven for fenofibrate).
	• Myositis, cholelithiasis, and cholecystitis can occur with fibric acid, and caution should be exercised with a history of liver disease.
	• The long-term effects of ezetimibe on cardiovascular morbidity and mortality are unknown. Ezetimibe is associated with a LDL-C lowering of about 18%, and additive LDL-C lowering occurs when used in combination with a statin.
	• The short-term tolerability of ezetimibe is similar to placebo, and the long-term safety is unknown.
	• Bile acid sequestrants reduce LDL-C by 15 to 30% and TG may increase 15%; therefore, are these agents are useful for patients with moderately elevated LDL-C. The effects of the bile acid sequestrants are apparent within one week and maximum at two to three weeks. Bile acid sequestrants are good for combination therapy and are most potent with a statin.
	• Bile acid sequestrants are not systemically absorbed; therefore, side effects are limited to the gastrointestinal tract. In addition, drug interactions are minimized by taking other medications one hour before the sequestrant or four hours after.
	
	<u>Combination therapy</u>
	• It has become common practice to adjust medication therapy, including using combinations of medications, to achieve LDL-C goals. Common combinations include statin/fibrate, statin/niacin, and statin/ezetimibe.
	    ○ A fibrate is commonly added to a statin, which results in enhanced lowering of LDL-C, as well as a higher incidence of myopathy.
	    ○ No published clinical trial to date has evaluated the clinical benefit of combination therapy with a statin and niacin on vascular events.
	    ○ The addition of ezetimibe to a statin significantly improves LDL-C over either agent alone. To date no large clinical trials have been completed evaluating this combination therapy

Clinical Guideline	Recommendation
	compared to statin monotherapy on clinical vascular endpoints. • Combinations of lipid-lowering agents do not improve clinical outcomes more than statin monotherapy. • Combination therapy can be considered on an individual basis, but the additional cost, complexity, and risk for side effects argue against routine use until further trials indicate what groups of patients might benefit. • There are negative trials of cholesterylester transfer protein inhibitors when used in combination with statins. • No randomized-controlled trials looking at clinical vascular endpoints are available for other agents such as fish oils or bile-acid sequestrants used in combination therapy. Lifestyle modifications • Patients who are overweight should be advised to reduce their caloric intake to achieve weight loss. • Patients should follow a diet and exercise program for a reasonable amount of time to determine whether their LDL-C level is lowered to the target range. • A diet low saturated and trans fats, and high in soluble fiber, with consideration given to adding two grams of plant sterol/stanol is recommended. • Vitamin E supplementation should not be used. • Light to moderate consumption of alcohol may lower CHD rates. • Omega-3 fatty acids should be recommended in patients with dyslipidemia (one gram of EPA/DHA by capsule supplement, or by eating at least two servings per week of fatty fish).
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association[14] (2007)**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice[15] (2012)**	Drugs • Currently available lipid-lowering drugs include statins, fibrates, bile acid sequestrants, niacin, and selective cholesterol absorption inhibitors (e.g., ezetimibe). • Statins, by reducing LDL-C, reduce cardiovascular morbidity and mortality as well as the need for coronary artery interventions. • Statins should be used as the drugs of first choice in patients with hypercholesterolemia or combined hyperlipidemia. • Selective cholesterol absorption inhibitors are not used as monotherapy

Clinical Guideline	Recommendation
	to decrease LDL-C. • Bile acid sequestrants also decrease TC and LDL-C, but tend to increase TG. • Fibrates and niacin are used primarily for TG lowering and increasing HDL-C, while fish oils (omega-3 fatty acids) in doses of 2 to 4 g/day are used for TG lowering. • Fibrates are the drugs of choice for patients with severely elevated TG, and prescription omega-3 fatty acids might be added if elevated TG is not decreased adequately. Drug combinations • Patients with dyslipidemia, particularly those with established CVD, diabetes, or asymptomatic high risk patients, may not always reach treatment targets; therefore, combination treatment may be needed. • Combinations of a statin and a bile acid sequestrants or a combination of a statin and ezetimibe can be used for greater reduction in LDL-C than can be achieved with either agent used as monotherapy. • Another advantage of combination therapy is that lower doses of statins can be utilized, thus reducing the risk of adverse events associated with high dose statin therapy. However, statins should be used in the highest tolerable dose to reach LDL-C target level before combination therapy is initiated. • Combinations of niacin and a statin increase HDL-C and decrease TG better than either drug used as monotherapy, but flushing is the main adverse event with niacin, which may affect compliance. • Fibrates, particularly fenofibrate, may be useful, not only for decreasing TG and increasing HDL-C, but can further lower LDL-C when administered in combination with a statin. • If target levels cannot be reached with maximal doses of lipid-lowering therapy or combination therapy, patients will still benefit from treatment to the extent to which dyslipidemia has been improved. In these patients, increased attention to other risk factors may help to reduce total risk.
National Institute for Health and Clinical Excellence: **Lipid Modification[16] (2010)**	• Statin therapy is recommended as part of the management strategy for the primary prevention of cardiovascular disease for adults who have a ≥20% 10 year risk of developing cardiovascular disease. • Treatment for the primary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. Higher intensity statins should not routinely be offered to people for the primary prevention of cardiovascular disease. • Fibrates, nicotinic acid or anion exchange resins should not routinely be offered for the primary prevention of cardiovascular disease. If statins are not tolerated, these treatments may be considered. • The combination of an anion exchange resin, fibrate, nicotinic acid or a fish oil supplement with a statin should not be offered for the primary prevention of cardiovascular disease. • Statin therapy is recommended for adults with clinical evidence of cardiovascular disease. People with acute coronary syndrome should be treated with a higher intensity statin. • Treatment for the secondary prevention of cardiovascular disease should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen. In people

Clinical Guideline	Recommendation
	taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy if a total cholesterol of <4 mmol/L (<155 mg/dL) or LDL-C <2 mmol/L (<77 mg/dL) is not attained. • Fibrates, nicotinic acid and anion exchange resins may be considered for secondary prevention in people with cardiovascular disease who are not able to tolerate statins. • People with primary hypercholesterolemia should be considered for ezetimibe treatment.
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[17] (2011)**	• Risk factor control for all patients with transient ischemic attack (TIA) or ischemic stroke: • Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD. • For patients with atherosclerotic ischemic stroke or TIA without known CHD, it is reasonable to target a reduction of ≥50% in LDL-C or a target LDL-C level <70 mg/dL to obtain maximal benefit. • Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to the National Cholesterol Education Program III guidelines (i.e., lifestyle modification, dietary guidelines, medication recommendations). • Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antilipemic agents are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Antilipemic Agents, Miscellaneous[2,8,18,19]

Indication	Niacin Extended-Release*	Niacin Immediate-Release*	Omega-3 Acid Ethyl Esters*
Hypertriglyceridemia			
Adjunctive therapy for the treatment of adult patients with severe hypertriglyceridemia who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control threm	✔	✔ †	
Adjunct to diet to reduce triglyceride (TG) levels in adults with severe (≥500 mg/dL) hypertriglyceridemia			✔
Primary Hypercholesterolemia and Mixed Dyslipidemia			
Adjunct to diet, alone or in combination with a bile acid binding resin, for reduction of elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia		✔	
Adjunct to diet and in combination with simvastatin or lovastatin for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with niacin	✔		

Indication	Niacin Extended-Release*	Niacin Immediate-Release*	Omega-3 Acid Ethyl Esters*
extended-release, simvastatin, or lovastatin monotherapy is considered inadequate			
Adjunct to diet to reduce elevated TC, LDL-C, apolipoprotein B, and TG levels, and to increase high-density lipoprotein cholesterol in patients with primary hyperlipidemia and mixed dyslipidemia	✔		
Adjunct to diet and in combination with a bile acid binding resin to reduce elevated TC and LDL-C levels in adult patients with primary hyperlipidemia	✔		
Secondary Prevention of Cardiovascular Disease			
Adjunct to diet to reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia	✔		
Adjunct to diet and in combination with a bile acid binding resin to slow progression or promote regression of atherosclerotic disease in patients with a history of coronary artery disease and hyperlipidemia	✔		

*Over-the-counter products are considered dietary supplements.
†Types IV and V hyperlipidemia.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antilipemic agents are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antilipemic Agents, Miscellaneous[20]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (minutes)
Niacin	ER: 60 to 76	Not reported	Liver (rapid; % not reported)	Renal (60 to 88)	IR: 20 to 45
Omega-3 acid ethyl esters	Not reported	Not reported	Not reported	Not reported	Not reported

ER=extended-release, IR=immediate-release

V. Drug Interactions

There are no significant drug interactions reported with the miscellaneous antilipemic agents.[2]

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antilipemic agents are listed in Table 5. Pooled data from randomized, placebo-controlled trials have shown that prescription omega-3 acid ethyl esters are safe and well tolerated.[9] At usual antilipemic dosages, niacin is generally well tolerated and side effects are mild and transient. The most common adverse effects with niacin are gastrointestinal upset, flushing and pruritus. Flushing is more common with the immediate-release formulation and may be diminished by starting with a low dose, taking niacin after meals, and by pretreating with aspirin or ibuprofen.[2,20] Sustained-release preparations have been shown to be hepatotoxic in doses ≥2 g per day. Cases of severe hepatic toxicity, including fulminant hepatic necrosis have occurred in patients who have substituted sustained-release niacin products for immediate-release products at equivalent doses.[18,19]

Table 5. Adverse Drug Events (%) Reported with the Antilipemic Agents, Miscellaneous[2,8,18,19]

Adverse Events	Niacin Extended-Release (Niaspan®)	Niacin Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters (Lovaza®)
Cardiovascular			
Angina pectoris	-	-	1
Arrhythmia	✔	✔	✔
Atrial fibrillation	✔	✔	-
Bypass surgery	-	-	✔
Cardiac arrest	-	-	✔
Chest pain	-	-	✔
Hypertension	-	-	✔
Hypotension	✔	✔	-
Migraine	✔	-	✔
Myocardial infarction	-	-	✔
Myocardial ischemia	-	-	✔
Occlusion	-	-	✔
Orthostasis	✔	✔	-
Palpitations	✔	-	-
Peripheral edema	✔	-	-
Peripheral vascular disorder	-	-	✔
Postural hypotension	✔	-	-
Syncope	✔	-	✔
Tachycardia	✔	-	✔
Central Nervous System			
Depression	-	-	✔
Dizziness	✔	-	✔
Emotional lability	-	-	✔
Facial paralysis	-	-	✔
Headache	-	✔	-
Insomnia	✔	-	✔
Migraine	✔	-	-
Nervousness	✔	-	-
Paresthesia	✔	-	-
Vasodilatation	-	-	✔
Vertigo	-	-	✔
Dermatologic			
Acanthosis nigricans	-	✔	-
Alopecia	-	-	✔
Dry skin	✔	✔	-
Eczema	-	-	✔
Flushing	63 to 69	✔	-
Hyperpigmentation	-	✔	-
Pruritus	3 to 8	✔	✔
Rash	0 to 5	-	2
Urticaria	✔	-	-
Skin burning sensation	✔	-	-
Skin discoloration	✔	-	-
Sweating	✔	-	✔
Endocrine and Metabolic			
Gout	✔	✔	-
Gastrointestinal			
Abdomen enlarged	-	-	✔
Anorexia	-	-	✔
Colitis	-	-	✔

Adverse Events	Niacin Extended-Release (Niaspan®)	Niacin Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters (Lovaza®)
Constipation	-	-	✔
Diarrhea	7 to 14	✔	-
Dry mouth	-	-	✔
Dyspepsia	-	✔	3
Dysphagia	-	-	✔
Eructation	✔	-	5
Fecal incontinence	-	-	✔
Flatulence	✔	-	-
Gastritis	-	-	✔
Gastroenteritis	-	-	✔
Increased appetite	-	-	✔
Intestinal obstruction	-	-	✔
Melena	-	-	✔
Nausea	4 to 11	-	-
Pancreatitis	-	-	✔
Peptic ulceration	✔	✔	-
Tenesmus	-	-	✔
Vomiting	0 to 9	✔	✔
Hematologic			
Prothrombin time increased	✔	-	-
Thrombocytopenia	✔	-	-
Hepatic			
Fulminant hepatic necrosis	-	✔	-
Hepatitis	✔	-	-
Hepatotoxicity	✔	✔	-
Jaundice	✔	✔	-
Laboratory Test Abnormalities			
Amylase increased	✔	-	-
Hyperglycemia	✔	✔	✔
Hyperlipidemia	-	-	✔
Hyperuricemia	✔	✔	-
Lactate dehydrogenase increased	✔	-	-
Liver function test abnormalities	✔	✔	✔
Phosphorus decreased	✔	-	-
Musculoskeletal			
Arthralgia	-	-	✔
Arthritis	-	-	✔
Asthenia	✔	-	✔
Back pain	-	-	2
Fracture	-	-	✔
Malaise	-	-	✔
Myalgia	✔	-	✔
Myasthenia	✔	-	-
Myopathy	✔	-	-
Neck pain	-	-	✔
Pain	-	-	2
Rhabdomyolysis	-	✔	-
Rheumatoid arthritis	-	-	✔
Tendon rupture	-	-	✔
Respiratory			
Asthma	-	-	✔
Bronchitis	-	-	✔

Adverse Events	Niacin Extended-Release (Niaspan®)	Niacin Immediate-Release (Niacor®)	Omega-3 Acid Ethyl Esters (Lovaza®)
Cough	2 to 8	-	✔
Dyspnea	✔	-	✔
Epistaxis	-	-	✔
Laryngitis	-	-	✔
Pharyngitis	-	-	✔
Pneumonia	-	-	✔
Rhinitis	-	-	✔
Sinusitis	-	-	✔
Urogenital			
Cervix disorder	-	-	✔
Endometrial carcinoma	-	-	✔
Epididymitis	-	-	✔
Impotence	-	-	✔
Other			
Anaphylaxis	✔	-	✔
Angioedema	✔	-	-
Blurred vision	✔	-	-
Body odor	-	-	✔
Cataract	-	-	✔
Chills	-	-	✔
Edema	-	-	✔
Facial edema	✔	-	-
Fever	-	-	✔
Flu symptoms	-	-	4
Hemorrhagic diathesis	-	-	✔
Hypersensitivity reactions	✔	-	-
Infection	-	-	4
Laryngismus	✔	-	-
Larynx edema	✔	-	-
Lymphadenopathy	-	-	✔
Macular edema	✔	✔	-
Neoplasm	-	-	✔
Sudden death	-	-	✔
Suicide	-	-	✔
Taste perversion	-	-	3
Tongue edema	✔	-	-
Toxoid amblyopia	-	✔	-

✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antilipemic agents are listed in Table 6.

Table 6. Usual Dosing Regimens for the Antilipemic Agents, Miscellaneous[8,18,19]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Niacin	Hyperlipidemia: Extended-release capsule: 1to 2 g two to three times daily; maximum, 6 g/day	Safety and efficacy in children have not been established (extended-release capsule, immediate-release).	Extended-release capsule: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Extended-release tablet: initial, 500 mg at bedtime; maintenance, 1,000 to 2,000 mg once daily; maximum, doses >2,000 mg/day are not recommended, in addition when administered as combination therapy the doses of lovastatin and simvastatin should not exceed 40 mg/day Tablet: initial, 250 mg/day with evening meal; maintenance, 1 to 2 g two or three times daily <u>Secondary prevention of cardiovascular disease:</u> Extended-release tablet: initial, 500 mg at bedtime; maintenance, 1,000 to 2,000 mg once daily; maximum, doses >2,000 mg/day are not recommended <u>Severe hypertriglyceridemia:</u> Extended-release capsule: 1to 2 g two to three times daily; maximum, 6 g/day Extended-release tablet: initial, 500 mg at bedtime; maintenance, 1,000 to 2,000 mg once daily; maximum, doses >2,000 mg/day are not recommended Tablet: initial, 250 mg/day with evening meal; maintenance, 1 to 2 g two or three times daily	Safety and effectiveness in children ≤16 years of age have not been established (extended-release tablet).	Extended-release tablet: 250 mg 500 mg 750 mg 1,000 mg Tablet: 50 mg 100 mg 250 mg 500 mg
Omega-3 acid ethyl esters	<u>Severe hypertriglyceridemia:</u> Capsule: 4 g/day taken as a single 4 g dose or as two 2 g doses (2 capsules given twice daily)	Safety and effectiveness in children have not been established.	Capsule: 1 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antilipemic agents are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Antilipemic Agents, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hypercholesterolemia				
Elam et al.[21] (2000) Niacin IR (Niacor®) 3,000 mg per day or maximum tolerated dosage vs placebo	MC, PC, RCT Patients with peripheral arterial disease with or without diabetes, mean age 67 years for patients with diabetes and 65 years for those without diabetes	N=468 (N=125 patients with diabetes) Up to 60 weeks (12-week active run-in and 48-week double-blind)	Primary: Change in lipid profile, glucose, HbA_{1c}, ALT, uric acid; hypoglycemic drug use, compliance, adverse events Secondary: Not reported	Primary: Niacin use significantly increased HDL-C by 29 and 29% and decreased TG by 23 and 28% and LDL-C by 8 and 9%, respectively, in participants with and without diabetes compared to baseline (P<0.001 for niacin vs placebo for all). Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL; P=0.04 and P<0.001) in participants with and without diabetes, respectively. HbA_{1c} levels were unchanged from baseline to follow-up in participants with diabetes treated with niacin. In participants with diabetes treated with placebo, HbA_{1c} decreased by 0.3% (P=0.04 for difference). There were no significant differences in niacin discontinuation, niacin dosage, or hypoglycemic therapy in participants with diabetes assigned to niacin vs placebo. Secondary: Not reported
Capuzzi et al.[22] (1998) Niacin ER (Niaspan®) titrated to 1 to 3 g per day Concomitant therapy with a statin, bile acid sequestrant or both	ES, MC, OL Patients with primary hypercholesterolemia who were previously enrolled in a randomized short-term study or in a placebo-only qualification clinical trial	N=517 Up to 96 weeks	Primary: Changes in LDL-C and apo B Secondary: Changes in TC, HDL-C, TC:HDL-C, Lp(a) and TG; adverse events	Primary: Patients receiving niacin experienced significant reductions in LDL-C by 18% at week 48 and 20% at week 96. Similar reductions were seen with apo B (16% at week 48 and 19% at week 96). The percent changes achieved by both 48 and 96 weeks of therapy were statistically significant (P<0.001). Secondary: HDL-C significantly increased by 26% at week 48 and 28% at week 96 in patients receiving niacin. TC modestly decreased (12 and 13%, respectively), whereas the TC:HDL-C ratio decreased by almost one third

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
was permitted if the patient did not achieve sufficient LDL-C reduction.				(P<0.001 for all). TG and Lp(a) levels were decreased by 27 and 30%, respectively, at week 48, and by 28 and 40%, respectively, at week 96 (P<0.001 for all). Niacin was generally well tolerated. Flushing was common (75%); however, there was a progressive decrease in flushing with time from 3.3 episodes in the first month to ≤1 episode by week 48. Aspirin was used by one third of patients before niacin dosing to minimize flushing episodes. Six percent of patients discontinued therapy due to flushing. Serious adverse events occurred in about 10% of patients; however, none were considered probably or definitely related to niacin. No deaths or myopathy occurred. There were statistically significant increases in alkaline phosphatase, ALT, amylase, AST, direct bilirubin, glucose, and uric acid and a decrease in phosphorus (P<0.001 for all). Mean platelet counts decreased by 10.1% at week 48 and 14.8% at week 96, whereas leukocyte counts increased by 6.5% and 6.8%, respectively, at week 48 and week 96 of therapy (P<0.0001 for all).
Guyton et al.[23] (1998) Niacin ER (Niaspan®) titrated to 1 to 3 g per day Concomitant therapy with a statin, bile acid sequestrant or both was permitted if the patient did not achieve sufficient LDL-C reduction.	ES, MC, OL Patients with primary hyperlipidemia who were previously enrolled in an RCT or in a placebo-only qualification clinical trial	N=269 patients treated up to 96 weeks and a cohort of N=230 patients treated for 3 months (safety data)	Primary: Changes in TC, LDL-C, HCL-C, TG, apo B and Lp(a); safety Secondary: Not reported	Primary: The dosages of niacin attained by 269 patients were 1,000 mg (95% of patients), 1,500 mg (86%) and 2,000 mg (65%). After 96 weeks of treatment, niacin alone (median dose 2,000 mg) significantly reduced LDL-C (18%), TC (10%), and TG (26%), and increased HDL-C (32%). Apo B and Lp(a) were significantly reduced by 26 and 36%, respectively, at 48 weeks but values for these parameters were not available at 96 weeks (P<0.01 for all). At 96 weeks of the study, niacin plus a statin significantly lowered LDL-C (32%), TC (24%), and TG (32%) and increased HDL-C (25%) (P<0.01 for all values). Apo B (26%; P<0.01) and Lp(a) (19%; P value not significant) were also reduced at 48 weeks but values for these parameters were not available at 96 weeks. Niacin plus a bile acid sequestrant lowered LDL-C (28%) and TC (15%)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and increased HDL-C (31%) (P<0.01 for all values). Niacin plus a bile acid sequestrant increased TG (5%; P value not significant). Apo B and Lp(a) were significantly reduced by 19 and 24% (P<0.01), respectively, at 48 weeks but values for these parameters were not available at 96 weeks. Intolerance to flushing led 4.8% of participants (13 of 269) to discontinue niacin. (Combining all of the data, 7.3% of patients discontinued niacin due to flushing.) Other medication-related adverse events leading to discontinuation from the 96-week study included nausea (3.3% of patients) sometimes with vomiting, other gastrointestinal symptoms (1.5%) and pruritus (2.6%). One case each of acanthosis nigricans, elevated glucose, gout, headache, palpitations and shoulder pain led to patient withdrawal. Overall, 9 of 499 (2.6%) patients experienced an ALT or AST elevation >2 times upper limit of normal. Five of these patients were on combination therapy, including four with a statin and one with a bile acid sequestrant. In five of the nine cases, the transaminase elevation resolved while niacin was continued without reduction in dose. Three cases led to niacin dosage reduction. One patient discontinued niacin because of transaminase elevations. Leg aches and myalgias with normal creatine kinase levels were described in one patient taking niacin with simvastatin. Secondary: Not reported
Gray et al.[24] (1994) Niacin SR (Slo-Niacin®) average maintenance dose of 1.67 g per day	RETRO Male veterans with dyslipoproteinemia who were treated with niacin	N=969 1 to 36 months	Primary: Changes in lipid profile, alterations in hepatic enzymes and blood chemistry tests, hepatotoxicity Secondary: Not reported	Primary: Lipoprotein responses were dose-related and favorable. Results included the following: TC -19.1%, LDL-C -24.0%, HDL-C 5.7%, and TG -32.5% (P≤0.0035 for all). Statistically but not clinically meaningful dose-related increases were seen in levels of liver enzymes and serum glucose (AST 29%, ALT 23%, alkaline phosphatase 25%, and glucose 7%; P=0.0001). Niacin was discontinued in 48.5% (435 of 896) of patients primarily because of adverse effects. The primary documented reasons for discontinuation included flushing and itching (8.9%), increased serum

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				glucose (4.8%), gastrointestinal complaints (3.7%) and increased liver function tests (3.7%). Poor glycemic controlled to discontinuation in 40.6% (43 of 106) patients with diabetes mellitus. Twenty of 896 (2.2%) and 42 of 896 (4.7%) patients met biochemical criteria for "probable" and for "possible or probable" niacin-induced hepatotoxicity, respectively. Predisposing factors included high dose, alcohol use, preexisting liver disease and concurrent oral sulfonylurea therapy. Secondary: Not reported
Grundy et al.[25] (2002) Niacin ER (Niaspan®) 1,000 mg per day vs niacin ER (Niaspan®) 1,500 mg per day vs placebo	DB, PC, RCT Patients with stable type 2 diabetes, 47% were receiving concomitant statin therapy	N=148 16 weeks	Primary: Change in HDL-C, TG, HbA_{1c} Secondary: TC, LDL-C, FBG, adverse effects	Primary: Dose-dependent increases in HDL-C (13 to 19% for the 1,000 mg dose and 22 to 24% for the 1,500 mg dose; both P<0.05 vs placebo) and reductions in TG levels (-15 to -20% for the 1,000 mg dose; P value not significant, and -28 to -36% for the 1,500 mg dose; P<0.05) were observed. Changes in HbA_{1c} levels from baseline to week 16 were no different for niacin 1,000 mg/day (7.28 and 7.35%; P=0.16) and placebo (7.13 and 7.11%) but were significantly different for niacin 1,500 mg/day (7.2 and 7.5%; P=0.048). Secondary: Mean LDL-C levels were not significantly different than baseline for the placebo and niacin 1,000 mg groups. In the niacin 1,500 mg group, LDL-C levels decreased at all time points and the difference vs placebo was statistically significant at weeks 12 and 16 (P<0.05). The mean changes from baseline at 16 weeks were 9, 5 and -7% in the placebo, niacin 1,000 mg and 1,500 mg groups, respectively. Similar trends were observed for TC with mean increases of 4% in both the placebo and niacin 1,000 mg groups and a decrease of -6% in the niacin ER 1,500 mg group. In both the niacin groups, an initial rise in FBG was observed between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				weeks 4 and 8 which returned to baseline by week 16. Four patients in the niacin group (3 patients were receiving 1,500 mg) discontinued participation because of inadequate glucose control. Rates of adverse events other than flushing were similar for the niacin and placebo groups. Flushing was reported by about 67% of patients receiving niacin ER and about 10% of patients receiving placebo. Four patients, including 1 patient in the placebo arm, withdrew from the study due to flushing. No hepatotoxic effects or myopathy was observed.
Kuvin et al.[26] (2006) Niacin ER (Niaspan®) initially 500 mg at bedtime for 2 weeks then 1,000 mg at bedtime vs placebo	PC, RCT Patients with stable CAD and LDL-C <100 mg/dL, all received concurrent statin therapy (>80% atorvastatin)	N=60 3 months	Primary: Changes in lipoproteins, HDL and LDL particle distribution and inflammatory markers Secondary: Not reported	Primary: Six patients did not complete the protocol, two discontinued treatment due to flushing, and four were lost to follow-up. Niacin significantly increased total HDL-C by 7.5% and decreased TG by 15% compared to baseline (P<0.005 for both), whereas TC and LDL-C remained unchanged. Compared to baseline values, the addition of niacin resulted in a 32% increase in large-particle HDL (P<0.001) and an 8% decrease in small-particle HDL (P=0.0032). Addition of niacin produced an 82% increase in large-particle LDL (P=0.09) and a 12% decrease in small-particle LDL (P=0.008). Niacin also favorably altered inflammatory markers with lipoprotein-associated phospholipase A2 and CRP levels decreasing by 20 and 15%, respectively, compared to baseline (P<0.05 for both). No significant changes from baseline were seen in any tested parameter in patients who received placebo. No major cardiovascular events were reported during the study in the treatment or placebo group. Secondary: Not reported
Knopp et al.[27]	DB, MC, PG, RCT	N=223	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1998) Niacin IR titrated to 3 g per day vs niacin ER (Niaspan®) titrated to 1.5 g per day vs placebo	Patients with hypercholesterolemia, average age 54 years	25 weeks (9 week lead-in period)	Change in LDL-C, FPG, uric acid, drug tolerance Secondary: Change in TC, TG, HDL-C, HDL sub-fractions, apo B, apo AI, apo E, and Lp(a)	LDL-C was significantly reduced by 12, 12 and 22%, respectively, by niacin ER 1.5 g at bedtime, niacin IR 1.5 g/day, and niacin IR 3.0 g/day, respectively, compared to placebo (P≤0.05). At equal doses of 1.5 g/day of niacin ER vs niacin IR, AST increased 5.0% vs 4.8% (P value not significant), FPG increased 4.8 vs 4.5% (P value not reported), and uric acid concentration increased 6 vs 16% (P=0.0001), respectively. Flushing events were more frequent with niacin IR vs niacin ER (1,905 vs 575; P<0.001). Flushing severity was slightly greater with SR niacin, but still well tolerated. Secondary: Compared to placebo at eight weeks, niacin SR 1.5 g at bedtime vs niacin IR 1.5 g/day showed comparable efficacy in lowering TC, TG, apo B, apo E and Lp(a), and raising HDL-C, HDL2-C, HDL3-C and apo AI (P≤0.05 in all instances). Niacin IR 3.0 g/day produced significantly greater changes in the above lipid parameters compared to niacin IR 1.5 g/day and niacin ER 1.5 g at bedtime (P≤0.05).
McKenney et al.[28] (1994) Niacin IR BID, for a total daily dose of 500, 1,000, 1,500, 2,000 and 3,000 mg for 6 weeks each vs niacin ER BID, for a total daily dose of 500, 1,000,	DB, PG, RCT Patients with LDL-C >160 mg/dL after 1 month on a NCEP ATP III-Step 1 diet	N=46 36 weeks	Primary: Changes in LCL-C, HDL-C and TG; adverse events Secondary: Not reported	Primary: Niacin ER significantly decreased LDL-C more than niacin IR with doses of ≥1,500 mg/day (P<0.04 or P<0.001). Niacin IR significantly increased HDL-C more than niacin ER with all doses (P<0.04 or P<0.001). The reductions in TG levels were similar between niacin IR and ER with all doses, except for niacin IR 1,000 mg/day which led to significantly greater reductions (P=0.009). Nine of 23 patients (39%) receiving niacin IR withdrew before completing the 3,000 mg/day dose. Four patients withdrew at 1,000 mg/day, one at 1,500 mg/day, three at 2,000 mg/day and one at 3,000 mg/day. The most common reasons for withdrawal were vasodilatory symptoms, fatigue and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
1,500, 2,000 and 3,000 mg for 6 weeks each				acanthosis nigricans. Eighteen of 23 patients (78%) receiving niacin ER withdrew before completing the 3,000 mg/day dose. Two patients withdrew at 1,000 mg/day, two at 1,500 mg/day, seven at 2,000 mg/day and seven at 3,000 mg/day. The most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue and increases in liver function tests, often with symptoms of hepatic dysfunction. None of the patients receiving niacin IR developed hepatotoxic effects, while 12 patients (52%) receiving niacin ER did. Secondary: Not reported
Superko et al.[29] (2004) Niacin IR 3,000 mg/day vs niacin ER (Niaspan®) 1,500 mg/day vs placebo Results of 38 patients receiving niacin ER 3,000 mg/day from a previous trial were utilized in this analysis.	PC, RCT Patients with hyper-cholesterolemia	N=218 14 weeks	Primary: Changes in lipid profile and Lp subclass distribution Secondary: Not reported	Primary: Niacin IR and ER significantly decreased TG, LDL-C, apo B and Lp(a), and significantly increased HDL-C ($P \leq 0.0001$ for all). Niacin IR and ER significantly increased mean LDL peak particle diameter and percent distribution of large LDL I and IIa, with a significant decrease in small LDL IIIa, IIIb, and IVb ($P<0.05$ for all, except for LDL I; $P=0.12$ for niacin ER). In general, the effects were greater in patients with LDL pattern B (predominance of dense LDL) compared to those with LDL pattern A (predominance of buoyant LDL). Compared to niacin IR, niacin ER 3,000 mg/day produced a smaller decrease in TG (-27 vs -47%; $P<0.001$), but had similar changes in LDL-C (-20 vs -22%; P value not reported), apo B (-22 vs -21%; P value not reported), HDL-C (27 vs 28%; P value not reported) and LDL peak particle diameter (0.90 vs 0.76 mm; P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Wi et al.[30] (2010) Niacin ER 500 mg/day for 5 weeks, followed by 1,000 mg/day for 4 weeks, followed by 1,500 mg/day vs fenofibrate 160 mg/day After discontinuation of any lipid modifying drug, patients entered an 8 week dietary run in period.	OL, RCT Patients 20 to 79 years of age with TG 150 to 499 mg/dL and HDL-C <45 mg/dL	N=201 24 weeks (includes 8 week dietary run in period)	Primary: Percent change from randomization to week 16 in apo B/apo AI Secondary: Percent changes in other lipid parameters, levels of glucose metabolism-related parameters, hsCRP	Primary: Apo B/apo AI was reduced with both treatments with no difference between the two (P=0.47). The percent reduction in apo B was greater with niacin, whereas the percent elevation in apo AI was higher with fenofibrate. Secondary: TC significantly decreased with both treatments, and TG decreased and HDL-C increased. LDL-C increased with fenofibrate but decreased with niacin. The percent reduction in TC was greater with niacin (P=0.01). TG decreased significantly more with fenofibrate (P=0.045), whereas the percent elevation in HDL-C was not different between the two treatments (P=0.22). The percent change in LDL-C was significantly different with the two treatments (P<0.001). Lp(a) levels were reduced with niacin only, and the change was significantly different compared to fenofibrate (P<0.001). FPG levels decreased with fenofibrate and increased significantly with niacin. HbA_{1c} levels increased with both treatments; the increase was borderline with fenofibrate and significant with niacin. The percent changes in FPG (P<0.001) and HbA_{1c} (P<0.001) levels were significantly different between the two treatments. Fasting insulin levels showed a borderline reduction with fenofibrate and a significant increase with niacin. HOMA-IR was decreased with fenofibrate and was increased with niacin. Percent changes of insulin (P<0.001) and HOMA-IR (P<0.001) were significantly different between the two treatments. hsCRP levels were significantly lowered with both treatments, but the percent change was greater with niacin (P=0.03).
Balasubramanyam et al.[31] (2011) Usual care vs	DB, PC, RCT Patients 21 to 65 years of age with hypertriglyceridemia (fasting TG >150 mg/dL) and receiving stable ART therapy	N=191 24 weeks	Primary: Baseline changes in lipid parameters Secondary: Baseline changes in insulin sensitivity,	Primary: Patients receiving fenofibrate achieved significant improvements in TG (P=0.002), TC (P=0.02), and non-HDL-C (P=0.003), compared to patients receiving niacin who achieved significant improvements in HDL-C (P=0.03), and both groups of patients achieved significant improvements in TC:HDL-C (P=0.005 and P=0.01). The combination of D/E plus fenofibrate plus niacin provided maximal benefit, reducing TG (-52% vs usual care; P=0.003), increasing HDL-C (12% vs usual care; P<0.001),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
low saturated fat diet and exercise (D/E) vs D/E and fenofibrate 145 mg/day (Tricor®) vs D/E and niacin SR 2,000 mg/day (Niaspan®) vs D/E and fenofibrate 145 mg/day and niacin SR 2,000 mg/day	for 6 months		glycemia, adiponectin, CRP, energy expenditure, and body composition	and decreasing non-HDL-C (-18.5% vs usual care; P=0.003) and TC:HDL-C (-24.5% vs usual care; P<0.001). Secondary: Of the secondary endpoints evaluated, there was an effect of niacin on FPG (P=0.0002), oral glucose tolerance test area under the curve for glucose (P=0.02), fasting insulin (P=0.03), HOMA-IR (P=0.008), insulin sensitivity index (P=0.007), and adiponectin (P<0.0001), and an effect of fenofibrate on creatinine (P=0.002).
Guyton et al.[32] (2000) Niacin ER (Niaspan®) titrated up to 1,000 mg at bedtime for 4 weeks, followed by 1,500 mg at bedtime for 4 weeks, followed by 2,000 mg at bedtime for 8 weeks	DB, MC, PC, RCT Patients 21 to 75 years of age with HDL-C ≤40 mg/dL, LDL-C ≤160 mg/dL or <130 mg/dL with atherosclerotic disease and TG ≤400 mg/dL	N=173 8 weeks	Primary: Effect on HDL-C Secondary: Change in other lipoproteins, adverse effects	Primary: Niacin 1,500 and 2,000 mg/day significantly increased HDL-C by 21 and 26%, respectively, compared to 13% with gemfibrozil (P<0.02). Secondary: Compared to gemfibrozil, niacin 1,500 and 2,000 mg/day significantly increased apo AI (9 and 11 vs 4%), reduced TC:HDL-C ratio (-17 and -22 vs -12%), reduced Lp(a) (-7 and -20 vs no change) and had no adverse effect on LDL-C (2 and 0 vs 9%; P<0.001 to P<0.02.). TG decreased by 40% with gemfibrozil compared to 16 and 29% with niacin 1,000 (P<0.001) and 2,000 mg/day (P<0.06). Effects on plasma fibrinogen levels were significantly favorable for niacin compared to gemfibrozil (-1 to -6% vs 5 to 9%, respectively; P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs gemfibrozil 600 mg BID				Flushing was significantly more frequent with niacin compared to gemfibrozil at every point (78 vs 10%; P values not reported). Flu syndrome occurred more frequently with niacin (P=0.006). Dyspepsia was more frequent with gemfibrozil (P=0.009).
Alrasadi et al.[33] (2008) Protocol 1 Fenofibrate 200 mg/day for 8 weeks vs atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID for 8 weeks Protocol 2 Fenofibrate 200 mg/day and atorvastatin 20 mg/day for 8 weeks vs niacin SR 1 g BID and atorvastatin 20 mg/day for 8 weeks	XO Men with HDL-C <5th percentile for age- and gender-matched patients and an identified genetic cause of HDL deficiency or ≥1 first degree relative affected with HDL deficiency	N=19 32 weeks	Primary: Percent changes in HDL-C and TC:HDL-C Secondary: Not reported	Primary: Protocol 1 The mean percent change in HDL-C was +6, -6, and +22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Only niacin significantly raised HDL-C (P<0.05). The mean percent change in TC/HDL-C ratio was +19, -26, and -22% in patients receiving fenofibrate, atorvastatin, and niacin, respectively. Both niacin and atorvastatin significantly lowered TC/HDL-C (P<0.05 and P<0.01, respectively). Protocol 2 The mean percent change in HDL-C was -2 and +18% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant increase in HDL-C (P<0.05). The mean percent change in TC:HDL-C was +32 and -32% in patients receiving fenofibrate plus atorvastatin and niacin plus atorvastatin, respectively. Only the group receiving niacin experienced a significant decrease in TC:HDL-C (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients in whom a statin was required were switched or maintained on atorvastatin 20 mg throughout the study in Protocol 2.				
Guyton et al.[34] (2008) Niacin ER 2 g (titrated) per day and ezetimibe-simvastatin 10-20 mg QD vs niacin ER 2 g (titrated) per day vs ezetimibe-simvastatin (E/S) 10-20 mg QD	DB, MC, RCT Patients 18 to 79 years of age with type IIa and IIb hyperlipidemia (LDL-C 130 to 190 mg/dL and TG ≤500 mg/dL)	N=1,220 24 weeks	Primary: Percent change from baseline in LDL-C, non-HDL-C, HDL-C, TG, TC, apo B, apo AI, and hsCRP Secondary: Not reported	Primary: After 24 weeks of therapy, the percent change from baseline in LDL-C, non-HDL-C, TG, apoB, TC:HDL-C, LDL-C:HDL-C, apo B:apo AI, and non-HDL-C:HDL-C were greater with niacin + E/S compared to treatment with niacin or E/S (P<0.001 for all). The percent change in HDL-C from baseline was significantly greater with niacin plus E/S compared to E/S (P<0.001). There was no significant difference with niacin plus E/S and niacin monotherapy (P>0.05). The percent change in TC from baseline was significantly greater with niacin plus E/S compared to niacin (P<0.001). There was no significant difference with niacin plus E/S and E/S monotherapy. The percent change in apoAI from baseline was significantly greater with niacin + E/S compared E/S (P<0.001). There was no significant difference with niacin + E/S and niacin monotherapy (P>0.05). Treatment with niacin + E/S led to a greater reduction in hsCRP compared to niacin monotherapy (P<0.005). Adverse events occurred more frequently in patients treated with niacin monotherapy and niacin + E/S compared to E/S monotherapy. This difference was due to flushing-related AEs in the niacin groups. Secondary: Not reported
Zhao et al.[35]	ES	N=160	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Niacin 2.4±2.0 g/day (mean dose) plus simvastatin 13±6 mg/day (mean dose) vs antioxidants (vitamin E 800 IU/day, vitamin C 1,000 mg/day, beta carotene 25 mg/day and selenium 100 µg/day) vs niacin plus simvastatin plus antioxidants vs placebo Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per	Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) including 25 with diabetes mellitus with mean LDL-C 128 mg/dL, HDL-C 31mg/dL and TG 217 mg/dL	38 months	Side effects, response to the question "Overall, how difficult is it to take the study medication?" Secondary: Not reported	Patients receiving niacin plus simvastatin experienced similar frequencies of clinical or laboratory side effects compared to placebo; any degree of flushing (30 vs 23%; P value not significant), symptoms of fatigue, nausea and/or muscle aches (9 vs 5%; P value not significant), AST at least three times the upper limit of normal (3 vs 1%; P value not significant), CPK at least two times the upper limit of normal (3 vs 4%; P value not significant), new onset of uric acid ≥7.5 mg/dL (18 vs 15%; P value not significant) and homocysteine ≥15 µmol/L (9 vs 4%; P value not significant). There were no side effects attributable to the antioxidant regimen. Glycemic control among diabetics declined mildly with niacin plus simvastatin, but returned to pre-treatment levels at month eight and remained stable for the rest of the trial. Niacin plus simvastatin was repeatedly described by 91% of treated patients vs 86% of placebo subjects as "very easy" or "fairly easy" to take. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
day.				
McKenney et al.[36] (2007) COMPELL Rosuvastatin 10 mg/day for 4 weeks, followed by 20 mg/day for 4 weeks, followed by 40 mg/day vs atorvastatin 20 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by atorvastatin 20 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by atorvastatin 40 mg/day plus niacin SR 2,000 mg/day vs simvastatin 20 mg/day plus ezetimibe 10 mg/day for 8 weeks, followed by simvastatin 40 mg/day plus ezetimibe 10	MC, OL, PG, RCT Patients ≥21 years of age with hyper-cholesterolemia, eligible for treatment based on the NCEP ATP III guidelines, with 2 consecutive LDL-C levels within 15% of each other and mean TG ≤300 mg/dL	N=292 12 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in HDL-C non-HDL-C, TG, Lp(a) and apo B; side effects	Primary: Atorvastatin plus niacin SR, rosuvastatin plus niacin SR, simvastatin plus ezetimibe and rosuvastatin were associated with similar reductions in LDL-C (56, 51, 57 and 53%, respectively; P=0.093). Secondary: Atorvastatin plus niacin SR was associated with a significant increase in HDL-C compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (22, 10 and 7%, respectively; P≤0.05). There was no significant differences in the reduction of non-HDL-C from baseline with any treatment (P=0.053). Atorvastatin plus niacin SR was associated with a significant reduction in TG compared to simvastatin plus ezetimibe and rosuvastatin-containing therapy (47, 33 and 25%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in Lp(a) compared to simvastatin plus ezetimibe and rosuvastatin (20 mg)-containing therapy (-14, 7 and 18%, respectively; P≤0.05). Atorvastatin plus niacin SR was associated with a significant reduction in apo B compared to rosuvastatin (43 vs 39%, respectively; P≤0.05). Side effects were similar across treatments (P values not reported). There were no cases of myopathy or hepatotoxicity reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs rosuvastatin 10 mg/day plus niacin SR 500 mg/day for 4 weeks, followed by rosuvastatin 10 mg/day plus niacin SR 1,000 mg/day for 4 weeks, followed by rosuvastatin 20 mg/day plus niacin SR 1,000 mg/day				
Fazio et al.[37] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day vs ezetimibe-simvastatin 10-20 mg/day At the end of 24 weeks, patients receiving niacin	DB, MC, RCT Patients 18 to 79 years of age with hyperlipidemia (Types IIa and IIb) with LDL-C 130 to 190 mg/dL, TG ≤500 mg/dL, creatinine <2 mg/dL, creatine kinase ≤2 times the upper limit of normal, transaminases ≤1.5 times the upper limit of normal and HbA_{1c} ≤8%	N=942 64 weeks	Primary: Safety and tolerability of ezetimibe/simvastatin plus niacin ER Secondary: Changes in HDL-C, TG, non-HDL-C and LDL-C	Primary: The most frequent reason for discontinuation was clinical adverse events related to niacin-associated flushing with ezetimibe/simvastatin plus niacin (0.7% for ezetimibe/simvastatin vs 10.3% for ezetimibe/simvastatin plus niacin). A significant number of patients receiving ezetimibe/simvastatin plus niacin discontinued because of low LDL-C levels <50 mg/dL (1.5 vs 7.1%). The overall incidence of clinical adverse events was slightly greater for ezetimibe/simvastatin plus niacin compared to ezetimibe/simvastatin owing to the greater number of patients who experienced drug-related clinical adverse events and drug-related discontinuations with ezetimibe/simvastatin plus niacin, mainly attributed to niacin-associated flushing and pruritis. The percentage of patients with consecutive elevations in ALT or AST of at least three times or greater the upper limit of normal, and creatine kinase of at least ten times or greater the upper limit of normal were low and comparable between treatments. A total of 19 patients had adverse events of increased FPG levels, with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ER were rerandomized to either one of the other 2 treatment regimens.				eight receiving ezetimibe/simvastatin and 11 receiving ezetimibe/simvastatin plus niacin. Secondary: Ezetimibe/simvastatin plus niacin significantly improved baseline HDL-C, TG, non-HDL-C, LDL-C, apo B, apo AI and Lp ratios compared to ezetimibe/simvastatin at week 64 (P<0.004). The changes in TC were comparable between the two treatment groups and the reduction in hsCRP was numerically greater with ezetimibe/simvastatin plus niacin (P value not reported). Ezetimibe/simvastatin plus niacin increased HDL-C considerably during the first 16 weeks of treatment, and at a lower, but significant, rate from 16 to 24 weeks, and then remained constant throughout 64 weeks. The HDL-C change was significantly greater with ezetimibe/simvastatin plus niacin vs ezetimibe/simvastatin throughout the 64 weeks (P<0.001). The reductions in LDL-C, non-HDL-C and TG observed after four weeks with ezetimibe/simvastatin plus niacin were maintained throughout the 64 weeks. In contrast, the levels remained relatively stable with ezetimibe/simvastatin throughout the 64 weeks (P<0.001) and became significant for non-HDL-C after eight weeks (P=0.002) and LDL-C after 12 weeks (P<0.001).
Fazio et al.[38] (2010) Ezetimibe-simvastatin 10-20 mg/day plus niacin ER 2 g/day vs niacin ER 2 g/day vs ezetimibe-simvastatin 10-20 mg/day	Subgroup analysis Hyperlipidemic patients with diabetes mellitus, metabolic syndrome without diabetes mellitus or neither	N=765 at 24 weeks N=574 at 64 weeks	Primary: Changes in HDL-C, TG, non-HDL-C, LDL-C, fasting glucose and uric acid Secondary: Not reported	Primary: The effect of triple therapy on efficacy variables across patient subgroups was generally consistent with the significantly greater improvements observed in the total population compared to niacin and combination therapy. Triple therapy improved levels of LDL-C, other lipids and Lp ratios compared to niacin and combination therapy at 24 and 64 weeks. Triple therapy also increased HDL-C and Lp(a) comparably to niacin and more than combination therapy. Triple therapy also decreased hsCRP more effectively than niacin and comparably to combination therapy. Fasting glucose trended higher for niacin compared to combination therapy. Glucose elevations from baseline to 12 weeks were highest for patients with diabetes (niacin, 24.9 mg/dL; triple therapy, 21.2 mg/dL and combination therapy, 17.5 mg/dL). Fasting glucose levels then declined to pretreatment levels at 64 weeks in all subgroups. New onset diabetes was more frequent among patients with metabolic

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
At the end of 24 weeks, patients receiving niacin ER were rerandomized to either one of the other 2 treatment regimens.				syndrome than those without for the first 24 weeks and trended higher among those receiving niacin (niacin, 5.1%; combination therapy, 1.7% and triple therapy, 8.8%). Between weeks 24 and 64, five and one additional patient(s) receiving combination (cumulative incidence, 5.9%) and triple therapy (cumulative incidence, 9.2%) were diagnosed with diabetes. Treatment-incident increases in uric acid were higher among patients receiving niacin, but there were no effects on symptomatic gout. Secondary: Not reported
Pownall et al.[39] (1999) Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, PG, RCT Patients with severe hypertriglyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks	Primary: Effect on TG, lipid profile, and lipid composition Secondary: Not reported	Primary: Median TG levels were reduced 38.9% from baseline in the omega-3 acid ethyl ester group compared to 7.8% with placebo (P=0.001). Omega-3 acid ethyl esters also significantly reduced TC (-9.9%; P=0.004) and VLDL-C (-29.2%; P=0.001) and significantly increased LDL-C (16.7%; P=0.007) from baseline. HDL-C increased in patients receiving omega-3 acid ethyl esters (5.9%; P=0.057 vs baseline and P=0.023 vs placebo) and decreased in patients receiving placebo (-5.9%; P value not significant vs baseline). Secondary: Not reported
McKeone et al.[40] (1997) Omega-3 acid ethyl esters (Omacor®*) 4 g per day vs placebo	DB, PC, RCT Patients with severe hypertriglyceridemia (TG ≥500 mg/dL but <2,000 mg/dL)	N=40 12 weeks	Primary: Effect on TG and serum phospha-tidylcholine Secondary: Changes in lipid profile	Primary: Treatment with omega-3 acid ethyl esters significantly reduced TG levels by 26% compared to a 7% increase for placebo. Incorporation of eicosapentaenoic and docosahexaenoic acid into the serum phosphatidylcholine occurred within 6 weeks and was usually accompanied by a reduction in plasma TG. Secondary: Omega-3 acid ethyl esters also significantly reduced VLDL-C (28%) and TC (11%), and increased HDL-C (14%). None of these parameters significantly changed in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Calabresi et al.[41] (2000) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks vs placebo for 8 weeks	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 26 weeks	Primary: Changes in lipid profile and LDL-C subclass distribution Secondary: Safety	Primary: Omega-3 acid ethyl esters significantly lowered plasma TG and VLDL-C by 27 and 18%, respectively (both P<0.05) compared to baseline. TC and HDL-C did not change but LDL-C and apo B increased by 21% (P=0.05) and 6% compared to baseline (P<0.05). Omega-3 acid ethyl esters treatment caused a redistribution of LDL-C subclasses towards less dense lipoprotein particles (possibly indicative of a less atherogenic LDL-C profile); however, the average LDL-C size did not change. Secondary: Omega-3 acid ethyl esters were well tolerated with no reports of drug-related adverse events or negative safety parameters (e.g., glucose, uric acid, liver enzymes, kidney function, and platelet count).
Calabresi et al.[42] (2004) Omega-3 acid ethyl esters (Omacor®*) 4 g per day for 8 weeks vs placebo for 8 weeks	DB, RCT, XO Patients with familial combined hyperlipidemia	N=14 20 weeks	Primary: Changes in lipid profile, LDL-C and HDL-C subclass distribution Secondary: Not reported	Primary: Plasma TG were 44% lower and LDL-C and apo B were 25 and 7% higher after omega-3 acid ethyl esters than placebo (P<0.05 for all). HDL-C was higher (8%) after omega-3 acid ethyl esters than placebo but this difference did not reach statistical significance (P>0.05). Omega-3 acid ethyl esters caused a selective increase of the more buoyant HDL_2-C subfraction; plasma HDL_2-C and total mass increased by 40% (P<0.05) and 26%, respectively, whereas HDL_3-C and total mass decreased by 4% (P>0.05) and 6%. The plasma concentration of the HDL-bound antioxidant enzyme paraoxonase increased by 10% after omega-3 acid ethyl esters (P<0.05). Secondary: Not reported
Bays et al.[43] (2010) Omega-3 acid ethyl ester (Lovaza®) 4 g/day	DB, MC, PC, RCT Patients 18 to 79 years of age with hypercholesterolemia (non-HDL-C >160	N=245 16 weeks	Primary: Percent change in non-HDL-C level between baseline and week eight	Primary: After eight weeks of therapy, the median percent change in non-HDL-C was -40.2% in the omega-3 acid ethyl ester group and -33.7% in the placebo group (90% CI, -7.2 to -2.9; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo All patients received atorvastatin 10 mg/day for 8 weeks, 20 mg for 4 weeks, and 40 mg for 4 weeks.	mg/dL and TG 250 to 599 mg/dL)		Secondary: Percent changes in non-HDL-C level between baseline and the end of treatment with atorvastatin at 20 mg and 40 mg, percent changes in TC, HDL-C, LDL-C, VLDL-C, TG, apo AI and apo B concentrations	Omega-3 acid ethyl ester significantly reduced non-HDL-C compared to placebo during the atorvastatin 20 mg phase (-7.9%; 90% CI, -9.1 to -4.9; P<0.001) and atorvastatin 40 mg phase (-4.1%, 90% Cl, -6.8 to -2.4; P<0.001). There was no significant difference in the percentage of patients who achieved LDL-C goals with omega-3 acid ethyl ester (85.7%) or placebo groups (91.5%; P=0.20). There was no significant difference in the percentage of patients who achieved non-HDL-C goals with omega-3 acid ethyl ester (88.7%) or placebo groups (87.8%; P>0.99). Treatment with omega-3-acid ethyl esters with all doses of atorvastatin significantly reduced TC (P<0.001), TC:HDL-C (P<0.001), TG (P<0.001), VLDL-C (P<0.001), RLP-C (P<0.001) and increased HDL-C (P<0.001) compared to treatment with placebo with all doses of atorvastatin. There was no significant difference in LDL-C, apo AI, or apo B between the treatment groups. There was no significant difference in adverse events among the treatment groups.
Durrington et al.[44] (2001) <u>Phase I</u> Omega-3 acid ethyl esters (Omacor*) 2 g BID for 24 weeks vs placebo for 24 weeks All patients received simvastatin.	DB, RCT Patients ≤75 years of age with established CHD who were already receiving treatment with simvastatin 10 to 40 mg daily and who had TG >203 mg/dl	N=59 48 weeks	Primary: Percent change in TG and VLDL-C, as well as effects on other lipid parameters Secondary: Not reported	Primary: Serum TG and VLDL-C significantly decreased with omega-3 acid ethyl esters compared to baseline or placebo (20 to 30% reduction; P<0.0005 and 30 to 40% reduction; P<0.005, respectively). There were no adverse effects on other lipid parameters with omega-3 acid ethyl esters, including LDL-C and HDL-C. There were no significant adverse events with omega-3 acid ethyl esters. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Phase II Omega-3 acid ethyl esters (Omacor*) 2 g BID and simvastatin 10 to 40 mg QD for 24 weeks				
Nordoy et al.[45] (1998) Omega-3 acid ethyl esters (Omacor*) 4 g per/day vs placebo All patients received simvastatin 20 mg QD.	DB, PC, RCT Patients 25 to 60 years of age with combined hyperlipidemia receiving simvastatin 20 mg for 5 to 10 weeks	N=41 5 weeks	Primary: Lipid and lipoprotein parameters Secondary: Not reported	Primary: The addition of omega-3 acid ethyl esters to simvastatin therapy led to an increase in EPA (P<0.0002) and DHA (P<0.0003) and reduction in linoleic acid (P=0.001). The addition of omega-3 acid ethyl esters to simvastatin led to a reduction in TC (P=0.052) and TG (P<0.001). There was no significant effect on HDL-C with omega-3 acid ethyl esters. There was no effect on apo A1 or apo B with the addition of omega-3 acid ethyl esters to simvastatin; however, there was a significant reduction in the concentration of apo E (P=0.035). Secondary: Not reported
Davidson et al.[46] (2007) Omega-3-acid ethyl ester (Lovaza®) 4 g/day vs placebo All patients were	DB, MC, PC, PG, RCT Adult patients who have received ≥8 weeks of stable statin therapy and have a mean fasting TG ≥200 and <500 mg/dL and mean LDL-C below or within 10% NCEP	N=254 16 weeks (includes 8 weeks OL treatment with simvastatin)	Primary: Change in non-HDL-C Secondary: Changes in TG, VLDL-C, LDL-C, HDL-C, TC and apo B; adverse events	Primary: At the end of treatment, the median percent change in non-HDL-C was significantly greater with omega-3-acid ethyl esters compared to placebo (-9.0 vs -2.2%; P<0.001). Secondary: Treatment with omega-3-acid ethyl esters was associated with significant reductions in TG (2.9 vs 6.3%), VLDL-C (27.5 vs 7.2%) and TC:HDL-C ratio (9.6 vs 0.7%), and a significant increase in HDL-C (3.4 vs -1.2%) (*P*<0.001 for all). Adverse events reported by at least one percent of patients treated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
receiving simvastatin 40 mg/day.	ATP III goal			omega-3-acid ethyl esters that occurred with a higher frequency than those receiving simvastatin monotherapy were nasopharyngitis (3.3%), upper respiratory tract infection (3.3%), diarrhea (2.5%) and dyspepsia (2.5%). There was no significant difference in the frequency of adverse events between treatment groups. No serious adverse events were considered treatment related.
Maki et al.[47] COMBOS Omega-3-acid ethyl esters (Lovaza®) 4 g/day vs placebo All patients received simvastatin 40 mg/day.	DB, PC, RCT Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥8 weeks prior to trial enrollment	N=256 8 weeks	Primary: Non-HDL-C levels Secondary: TG, VLDL-C, LDL-C and HDL-C levels	Primary: Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest (<80.4 mg/dL), middle (80.4 to <99.0 mg/dL) and highest (≥99.0 mg/dL) tertiles achieved a percent change from baseline in non-HDL-C of the following: -5 vs 0%, -13 vs -4% and -11 vs -2% (P values not reported). Secondary: Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in TG of the following: -27 vs -8%, -32 vs -5% and -30 vs -6% (P values not reported). Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest (≥99.0 mg/dL) tertiles achieved a percent change from baseline in VLDL-C of the following: -27 vs -7%, -28 vs -10% and -29 vs -7% (P values not reported). Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in LDL-C of the following: 9.5 vs 1.1%, -0.9 vs -3.8% and -6.4 vs -4.5% (P values not reported). The baseline LDL-C tertile had a significant interaction with treatment for the LDL-C response (P=0.022). Use of omega-3-acid ethyl esters and placebo in patients with a baseline LDL-C in the lowest, middle and highest tertiles achieved a percent change from baseline in HDL-C of the following: 4 vs -1%, 2 vs -1% and 4 vs -1% (P values not reported).
Bays et al.[48] (2010)	ES, OL of COMBOS	N=188	Primary: The difference	Primary: The percent change in non-HDL-C from COMBOS end of treatment to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
COMBOS Omega-3-acid ethyl esters (Lovaza®) 4 g/day plus simvastatin 40 mg/day Patients who received placebo in the COMBOS trial were switched to OL treatment with omega-3-acid ethyl esters plus simvastatin (Switchers). Those who received omega-3-acid ethyl esters plus simvastatin in the COMBOS trial were maintained on current therapy (Nonswitchers) All patients continued therapeutic lifestyle changes diet.	Patients 18 to 79 years of age who had been receiving stable dose statin therapy for ≥8 weeks prior to trial enrollment	Up to 24 months	between Nonswitchers and Switchers in median percent change in non-HDL-C from COMBOS end of treatment to month four Secondary: Difference in the median percent change in non-HDL-C from COMBOS end of treatment to month 12 and 24; the change in non-HDL-C from COMBOS baseline to months four, 12 and 24 and from COMBOS end of treatment to months four, 12 and 24; percent changes in TC, HDL-C, LDL-C, VLDL-C, TG and TC:HDL-C for the same time points; HbA_{1c} levels	month four revealed a greater response among Switchers when compared to Nonswitchers. At month four, the median percent change in non-HDL-C from the end of DB treatment was -9.4% in Switchers and 0.9% in Nonswitchers (P<0.001). Secondary: After 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS end of treatment in Nonswitchers vs Switchers was -0.2 vs -0.64% (P=0.027) and 1.6 vs -6.3% (P=0.004). Reductions in non-HDL-C were maintained throughout the trial. After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in the total population was -8.3, -7.3 and -8.9%, respectively (P<0.001 for all). After four, 12 and 24 months of treatment, the median percent change in non-HDL-C from COMBOS baseline in Nonswitchers vs Switchers was -5.4 vs -10.3% (P=0.062), -6.6 vs -8.1% (P=0.604) and -7.8 vs -9.0% (P=0.496). Consistent with the non-HDL-C response, comparisons of the changes from the COMBOS end of treatment to months four, 12 and 24 in TG and other lipoprotein lipid parameters generally revealed greater reductions in Switchers vs Nonswitchers. The comparisons of the change from COMBOS baseline to these same endpoints reveled generally nonsignificant differences between the two groups. Median percent reductions from COMBOS baseline in TG, TC and VLDL-C in the total population were maintained at months four, 12 and 24 of treatment (P<0.001 for all). Omega-3-acid ethyl esters produced small median percent increases from baseline LDL-C levels at months four, 12 and 24. Among the subset of patients who had HbA_{1c} measured at baseline (n=38), the median absolute change in HbA_{1c} after 24 months of treatment was 0.1% (P value not reported).
Maki et al.[49] (2008) Omega-3 acid	RCT, XO Patients 18 to 79 years of age with	N=40 12 weeks	Primary: Lipid and lipoprotein parameters	Primary: Treatment with omega-3 acid ethyl esters resulted in a -40% reduction in non-HDL-C compared to -34% with placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ethyl esters (Lovaza®) 4 g/day vs placebo All patients received simvastatin 20 mg/day.	mixed dyslipidemia (TG 200 to 600 mg/dL and non-HDL-C above NCEP ATP III goal)		Secondary: Not reported	Treatment with omega-3 acid ethyl esters resulted in significantly greater changes in other lipid parameters compared to placebo, including VLDL-C (-42 vs -22%, respectively), TG (-44 vs -29%, respectively), TC (-31 vs -26%, respectively), and HDL-C (-16 vs -11%, respectively; P<0.05 for all). There was no significant difference in LDL-C with omega-3 acid ethyl esters (-37%) and placebo (-38%; P=0.433). Treatment with omega-3 acid ethyl esters resulted in significantly greater changes in other lipoprotein parameters compared to placebo, including apo B (-32 vs -28%, respectively), TC:HDL-C ratio (-39 vs -33%, respectively), and TG:HDL-C ratio (-51 vs -37%, respectively). There was no significant difference in apo AI levels with omega-3 acid ethyl esters (0.9) and placebo (4.3%; P=0.667). Secondary: Not reported
Peters et al.[50] (2012) Omega-3 PUFA vs placebo All patients were allowed to receive fenofibrate or niacin.	DB, MC, PC, RCT HIV-infected adult patients receiving HAART therapy and a fasting TG level 3.39 to 11.3 mmol/L	N=48 12 weeks	Primary: Change in baseline mean fasting TG, biochemical and virologic safety parameters Secondary: Safety	Primary: Omega-3 PUFA reduced TG by a mean of 1.75 mmol/L vs a 0.41 mmol/L increase with placebo (baseline-corrected percentage change related to placebo 95% CI, -69.48 to -6.53; P=0.019). No effect was observed on biochemical or virologic safety parameters. Secondary: No severe treatment-emergent adverse events occurred. Mild to moderate treatment-emergent adverse events were reported in 20 and 19 patients receiving omega-3 PUFA and placebo. Most treatment-emergent adverse events were gastrointestinal-related and included diarrhea, nausea, and flatulence.
Roth et al.[51] (2009) <u>Phase I</u> Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-	DB, MC, PC, RCT Patients 18 to 79 years of age with Fredrickson type IV dyslipidemia, BMI 25 to 43 kg/m^2, and TG 500 to 1,300	N=167 16 weeks	Primary: Median percent change in TG Secondary: Additional lipid and cardiovascular risk factors	Primary: After eight weeks of therapy, median TG values were reduced from 649.5 to 267.5 mg/dL (-60.8%) with P-OM3 + FENO and from 669.3 to 310 mg/dL (-53.8%) with FENO monotherapy (P=0.059). There was no significant difference between the treatment groups (P=0.059). Secondary: LDL-C was significantly increased with P-OM3 + FENO compared to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
OM3) QD for 8 weeks vs fenofibrate 130 mg (FENO) QD and placebo for 8 weeks Phase II Fenofibrate 130 mg (FENO) QD and omega-3 acid ethyl esters 4 g (P-OM3) QD for 8 weeks	mg/dL			FENO monotherapy (48.2 vs 39.0%, respectively; P=0.030). There was no significant difference in non-HDL-C among the treatment groups (-8.2% for P-OM3 + FENO vs -7.1% for FENO; P=0.767). There was a greater reduction in VLDL-C with P-OM3 + FENO than with FENO monotherapy (-57.6 vs -47.6%, respectively; P=0.016). There was a greater reduction in RLP-C with P-OM3 + FENO than with FENO monotherapy (-72.0 vs -62.1%; P=0.029). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly reduced TGs compared to the end of the DB treatment period (-17.5%; P=0.003). In the first eight week ES, the addition of P-OM3 to FENO monotherapy significantly increased LDL-C (+8.1%; P=0.001) compared to the group previously receiving P-OM3 + FENO (+0.4%). There was no significant change in non-HDL-C following the addition of P-OM3 to FENO. VLDL-C and RLP-C were significantly reduced by the addition of P-OM3 (-15.4%; P=0.030 and -25.8%; P=0.035, respectively). There was no significant difference in final lipid results for those who received P-OM3 + FENO for 16 weeks and those in which P-OM3 was added to FENO monotherapy during the OL phase of the study. In the pooled analysis of all patients enrolled in the eight week OL extension phase, the overall reductions of TGs and VLDL-C were -60.0 and -56.5%, respectively (P<0.001 for both). Non-HDLC and TC were also significantly reduced (P<0.001) over the 16 week treatment period in the pooled analysis. LDL-C increased 52.2% (P<0.001). There was no significant change in apo B at the end of the 16 week treatment study (P=0.544). The treatments were generally well tolerated and there was no significant difference in the safety profiles. The most adverse events were upper respiratory infection, nausea, diarrhea, constipation, gastroenteritis,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				dyspepsia, and headache.
Koh et al.[52] (2012) Omega-3 fatty acids 2 g/day vs fenofibrate 160 mg/day vs placebo	PC, PG, RCT, SB Patients with primary hypertriglyceridemia (>150 mg/dL)	N=50 2 months	Primary: Change in baseline lipid profile; change in baseline vasomotor function, hsCRP, and fibrinogen; change in baseline adiponectin, HbA_{1c}, and insulin resistance Secondary: Not reported	Primary: Placebo treatment significant reduced TG and TG:HDL-C, but increased LDL-C from baseline. Omega-3 fatty acids significantly reduced TG and TG:HDL-C from baseline. Fenofibrate significantly reduced T C, TG, apo B, TG:HDL-C, and non-HDL-C, and increased HDL-C and apo AI from baseline. Effects of fenofibrate on TC and T G were both significant compared to placebo (P<0.05). The magnitude of change in HDL-C, apo AI, TG:HDL-C, and non-HDL-C were significantly different when omega-3 fatty acids and fenofibrate therapy were compared, but both treatments resulted in comparable improvements in TG (P<0.05). Placebo did not significantly improve flow-mediated dilator response to hyperemia, but omega-3 fatty acids and fenofibrate significantly improved flow-mediated dilator response to hyperemia after two months when compared to baseline (P<0.001), and when compared to placebo (P<0.001). Brachial artery dilator responses to nitroglycerin were not significantly different between any of the therapies. Placebo and omega-3 fatty acids did not significantly change hsCRP and fibrinogen levels relative to baseline measurements. Fenofibrate significantly reduced hsCRP and fibrinogen levels after two months compared to baseline (P<0.001) or when compared to placebo (P<0.05). Omega-3 fatty acids did not significantly change insulin, plasma adiponectin levels, or insulin sensitivity compared to placebo. Compared omega-3 fatty acids, fenofibrate significantly decreased fasting insulin (P=0.023) and increased plasma adiponectin (P=0.002) and insulin sensitivity (P=0.015). Secondary: Not reported
Stalenhoef et al.[53] (2000) Omega-3 acid ethyl esters (Omacor*) 4 g per	DB, DD, RCT Patients with primary hyper-triglyceridemia	N=28 12 weeks	Primary: Change in lipid profile, LDL-C subfraction profile Secondary:	Primary: Both omega-3-acid ethyl esters and gemfibrozil resulted in similar and significant decreases in serum TG, VLDL-TG and VLDL-C concentrations and increases in HDL-C and LDL-C (P=0.05 to P<0.001 from baseline and P=0.29 to P=1.00 between groups).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
day vs gemfibrozil 1,200 mg per day			Not reported	Both therapies resulted in a more buoyant LDL-C subfraction profile (P=0.05 for omega-3-acid ethyl esters, P<0.01 for gemfibrozil and P=0.09 between groups in favor of gemfibrozil). Secondary: Not reported
van Dam et al.[54] (2001) Omega-3 acid ethyl esters (Omacor*) 4 g/day vs gemfibrozil 1,200 mg/day	DB, RCT Patients with hypertriglyceridemia (TG >400 mg/dL)	N=89 12 weeks	Primary: Percent change in TG Secondary: Percent change in TC, HDL-C, VLDL-C	Primary: The mean percent change in TG was -28.9% with omega-3 acid ethyl esters and -51.2% with gemfibrozil (P=0.007). Secondary: The mean percent change in HDL-C and TC were 1.2 and -10.2%, respectively, with omega-3 acid ethyl esters and 27.9 and -13.0%, respectively, with gemfibrozil (P=0.012 and P=0.513, respectively). The mean percent change in VLDL-C was -11.8% with omega-3 acid ethyl esters and -19.4% with gemfibrozil (P=0.494).
Trials Assessing Cardiovascular Outcomes				
Coronary Drug Project[55] (1975) Niacin IR 3,000 mg per day vs clofibrate 1.8 g per day vs placebo	DB, MC, PC, RCT Men 30 to 64 years of age with previous MI	N=8,341 5 years	Primary: All-cause mortality Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death), nonfatal cardiovascular events	Primary: The incidence of all-cause mortality was comparable between niacin (24.4%), clofibrate (25.5%) and placebo (25.4%) (P values not significant). Secondary: Five year rates of death due to cardiovascular disease were comparable between niacin (18.8%), clofibrate (17.3%) and placebo (18.9%) (P values not significant). Major cardiovascular events were reduced with niacin; CHD events by 13%, nonfatal MI by 27% and cerebrovascular events by 21%. Niacin significantly reduced the incidence of nonfatal MI compared to placebo (8.9 vs 12.2%; P<0.004). There was no evidence of significant efficacy of clofibrate with regard to all-cause and cause-specific mortality. Treatment with niacin for five years lowered TC by 10% and TG levels by

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				26% (P values not reported). Treatment with clofibrate lowered TC by 7% and TG levels by 22% (P values not reported).
Canner et al.[56] (1986) Coronary Drug Project Niacin IR 3,000 mg per day vs placebo	ES of the Coronary Drug Project Men 30 to 64 years of age with previous MI	N=8,341 9 years	Primary: All-cause mortality Secondary: Cause-specific mortality (e.g., coronary mortality and sudden death)	Primary: A follow-up of patients nine years after completion of the Coronary Drug Project trial (total mean follow up of 15 years) revealed that niacin reduced the risk of all-cause mortality by 11% (52.0 vs 58.2%; P=0.0004 vs placebo). Secondary: The survival benefit with niacin was primarily evident for death caused by CHD (36.5 vs 41.3%; P<0.05 vs placebo).
Lee et al.[57] (2009) Niacin ER (Niaspan®) 2,000 mg per day vs placebo	DB, PC, RCT Patients with pre-existing atherosclerosis and low HDL-C (<40 mg/dL) in whom LDL-C was treated with statins	N=71 1 year	Primary: Absolute change in carotid artery wall area and change in carotid plaque index Secondary: Not reported	Primary: Patients receiving niacin had a significantly greater change in carotid wall area at 12 months compared to placebo (difference -1.64 mm^2; 95% CI, -3.12 to -0.16; P=0.03). After 12 months of therapy, the change in carotid plaque index was significantly reduced by niacin compared to placebo (difference -0.016; 95% CI, -0.03 to -0.0022; P=0.02). Niacin increased HDL-C by 23% and decreased LDL-C by 19%. TG, apo B, and Lp(a) were significantly decreased by niacin compared to placebo. CRP was decreased by niacin compared to placebo (P=0.03 at six months and P=0.1 at 12 months). Adiponectin was significantly increased at both six and at 12 months (P<0.01). Secondary: Not reported
Taylor et al.[58] (2004) Niacin ER	DB, PC, RCT Adult patients with known CHD and low	N=167 1 year	Primary: Change in mean common CIMT after one year	Primary: After one year, mean CIMT increased significantly with placebo (0.044±0.100 mm; P<0.001) and was unchanged with niacin (0.014±0.104 mm; P=0.23).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(Niaspan®) 1,000 mg/day vs placebo All patients received background statin therapy.	levels of HDL-C (<45 mg/dL)		Secondary: Changes in lipid concentrations, composite of clinical cardiovascular events (including any hospitalization for an acute coronary syndrome, stroke, revascularization procedure or sudden cardiac death), adverse events	The overall difference in CIMT progression between placebo and niacin was not significant (P=0.08); however, a post hoc analysis revealed that niacin significantly reduced the rate of CIMT progression in subjects without insulin resistance (P=0.026). Secondary: HDL-C increased by 21% with niacin and did not change with placebo (P<0.003). Clinical cardiovascular events occurred in three patients receiving niacin (3.8%) and seven receiving placebo (9.6%; P=0.20). Adherence to trial medication based on pill counts ranged from 90.3 to 94.5%, and was not different between the two treatments (P value not reported). No patient experienced significant (three times the upper limit of normal) elevations of liver enzymes or developed myositis. At the end of the trial, skin flushing was reported in 69.2 and 12.7% of patients receiving niacin and placebo (P<0.001).
Illingworth et al.[59] (1994) Lovastatin 10 to 80 mg/day vs niacin IR 0.25 mg to 1.5 g TID	MC, OL, RCT Patients 21 to 75 years of age with primary hyper-cholesterolemia and either an LDL-C >160 mg/dL and CHD or ≥2 CHD risk factors without CHD or LDL-C >190 mg/dL without CHD or ≥2 risk factors after rigorous diet	N=136 26 weeks	Primary: Change from baseline in lipid parameters Secondary: Safety	Primary: Lovastatin reduced TC, LDL-C and apo B significantly more than niacin (P<0.01 for all). At weeks 10, 18 and 26, LDL-C was reduced by 26, 28 and 32% with lovastatin compared to five, 16 and 21% with niacin, respectively. The target treatment goal of LDL-C <130 mg/day for patients with CHD or less than two risk factors was achieved in 14, 19 and 35% of patients receiving lovastatin compared to zero, 18 and 26% of patients receiving placebo at weeks 10, 18 and 26, respectively (P values not significant). For the majority of those patients with CHD or two or more risk factors in whom the LDL-C goal was <110 mg/dL, neither drug was effective in achieving this goal. In these patients only 13 and 11% achieved this goal at week 26, respectively (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Niacin was more effective in decreasing TG at week 26 (P<0.01 vs lovastatin). Both treatments were effective in reducing VLDL-C, with no significant difference observed between the two treatments (P value not reported). Niacin produced reductions in Lp(a) of 14, 30 and 35% at weeks 10, 18 and 26, whereas lovastatin had no effect (P<0.05 or P<0.01 between drugs at each time point). Niacin was significantly more effective at increasing HDL-C and apo AI (P<0.01 vs lovastatin), except for the change in apo AI at week 10 (P value not reported). Niacin increased HDL-C by 20, 29 and 33% and apo AI by 11, 19 and 22% at weeks 10, 18 and 26. Lovastatin resulted in a modest increase in HDL-C and apo AI of 7 and 6%, respectively, at week 26. Secondary: Four deaths occurred in the trial, one with niacin and three with lovastatin. All were related to atherosclerosis, and none were deemed to be drug-related. Five and nine patients receiving lovastatin and niacin discontinued treatment because of adverse experiences (excluding deaths). For those who discontinued treatment, the reason was considered to be drug-related in four and eight patients receiving lovastatin and niacin (P value not significant). The major reasons for discontinuation of niacin were cutaneous complaints, including flushing, pruritis and rash. One patient discontinued lovastatin because of myalgias. Overall, patient tolerance to the treatments was better with lovastatin. Adverse events (in decreasing frequency) that occurred more frequently with niacin include flushing, paresthesia, pruritis, dry skin, nausea/vomiting, asthenia and diarrhea.
Sang et al.[60] (2009)	RCT Patients with clinical	N=108 12 months	Primary: All-cause mortality, MI,	Primary: At 12 months, clinical events included rehospitalization due to angina pectoris and heart failure attack, respectively, revascularization with PCI

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Atorvastatin 10 mg/day vs atorvastatin 10 mg/day and niacin ER	and angiographic criteria for coronary disease, with ≥50% stenosis of 1 coronary artery with high TC	(plus a 12 month follow up)	rehospitalization, revascularization with either PCI or CABG Secondary: Mean percent changes from baseline lipid parameters, effects on glucose metabolism, safety	and sudden death (7.14%) with atorvastatin. With combination therapy, the clinical events included rehospitalization due to heart failure attack, revascularization after PCI or CABG (5.77%). No significant reduction was observed with combination therapy (OR, 0.78; P=0.052). Secondary: TC, TG, LDL-C and Lp(a) levels decreased significantly with both treatments (P<0.01), with no significant difference between the two during the course of follow up (P>0.05). Apo A increased significantly with both treatments (P<0.01), with a more favorable effect observed with combination therapy (24.5 vs 40.8%; P<0.01). During the follow up, apo B fell by 5.63 (P<0.05 and 7.35% (P<0.01) with atorvastatin and combination therapy; with no significant difference between the two (P>0.05). During the trial, HDL-C levels increased by 11.67 (P<0.05) and 29.36% (P<0.01) with atorvastatin and combination therapy, with a significant difference favoring combination therapy (P<0.01). Niacin resulted in no significant increase in glucose levels at six or 12 months compared to baseline levels (P>0.05). In the subgroup of diabetic patients (n=28), niacin resulted in a significant increase in glucose levels at six months (P<0.01), and glucose levels increased more significantly at 12 months (P<0.01), but the effect of niacin was not significant in nondiabetic patients (P>0.05). HbA_{1c} levels did not show a significant increase at six months in patient with diabetes, but levels increased significantly at 12 months (P<0.05). Both treatments were generally well tolerated. The most common side effect of niacin therapy was flushing which appeared in four patients receiving combination therapy; however, all patients continued the medication and the flushing disappeared.
Taylor et al.[61] (2009) Niacin ER (Niaspan®) 2 g (titrated) QD	OL, PG, RCT Patients ≥30 years of age with atherosclerotic coronary or vascular disease or a CHD risk	N=208 14 months	Primary: Change in CIMT after 14 months Secondary: Change in lipid values, composite	Primary: Treatment with niacin led to a significant reduction in mean and maximal CIMT at eight months (P=0.001 and P=0.004, respectively) and 14 months (P=0.001 and P<0.001, respectively). There was no significant change in mean or maximal CIMT with ezetimibe at eight or 14 months compared to baseline. There was a significant difference between the niacin group and the ezetimibe group (P=0.003).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ezetimibe 10 mg QD	equivalent (diabetes mellitus, 10-year Framingham risk score ≥20%, coronary calcium score >200 for women or >400 for men who were receiving treatment with a statin (LDL-C <100 mg/dL and HDL-C <50 mg/dL for men or <55 mg/dL for women)		of major adverse cardiovascular events (MI, myocardial revascularization, admission to the hospital for an acute coronary syndrome, and death from CHD), discontinuation of study drug due to adverse effects, health-related quality of life	Secondary: The change in LDL-C in the ezetimibe group was -17.6 mg/dL compared to -10.0 mg/dL in the niacin group (P=0.01). The change in HDL-C in the ezetimibe group was -2.8 mg/dL compared to 7.5 mg/dL in the niacin group (P<0.001). There were significant reductions in TG in both groups. Major adverse cardiovascular events occurred in 5% of patients receiving ezetimibe compared to 1% of patients receiving niacin (P=0.04). Adverse drug effects led to withdrawal from the study in three of nine patients receiving ezetimibe and 17 of 27 patients receiving niacin (P=0.12). There was no significant difference between the two groups in the quality of life at baseline or at 14 months.
Brown et al.[62] (2001) HATS Niacin SR (Slo-Niacin®) titrated to 1 g BID and simvastatin vs antioxidants vs niacin SR (Slo-Niacin®) titrated to 1 g BID, simvastatin, and antioxidants	DB, PC Patients with clinical coronary disease (defined as previous MI, coronary interventions or confirmed angina) and with ≥3 stenoses of ≥30% of the luminal diameter or 1 stenosis of ≥50%, low HDL-C, normal LDL-C	N=160 3 years	Primary: Changes in lipid profile, arteriographic evidence of change in coronary stenosis (% stenosis caused by most severe lesion in each of nine proximal coronary segments), occurrence of first cardiovascular event (death from coronary causes, MI, stroke or revascularization) Secondary: Mean change in %	Primary: The mean levels of LDL-C, HDL-C, and TG were significantly changed by -42% (P<0.001), 26% (P<0.001) and -36% (P<0.001), respectively, in the niacin plus simvastatin group but were unaltered in the antioxidant only and placebo groups. Similar changes were observed when antioxidants were added to niacin plus simvastatin. The protective increase in HDL_2 (considered to be the most protective component of HDL-C) with niacin plus simvastatin (65%) was attenuated by concurrent therapy with antioxidants (28%; P=0.02). The average stenosis progressed by 3.9% with placebo, 1.8% with antioxidants (P=0.16 compared to placebo) and 0.7% with niacin plus simvastatin plus antioxidants (P=0.004), and regressed by 0.4% with niacin plus simvastatin (P<0.001). The frequency of the composite primary end point (death from coronary causes, MI, stroke or revascularization) was 24% with placebos, 3% with niacin plus simvastatin, 21% with antioxidants and 14% with niacin plus simvastatin plus antioxidants. The risk of the composite primary end point was 90% lower in the niacin plus simvastatin group than placebo

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo Patients whose HDL-C had not increased by prespecified amounts were switched to niacin IR (Niacor®) titrated to 4 g per day.			stenosis in lesions of varying degrees of severity, mean change in luminal diameter in proximal lesions and all lesions	(P=0.03). The risk in the other treatment groups did not differ significantly from that in the placebo group. Secondary: In general, the treatment effects observed with respect to the primary angiographic end point were confirmed for the various subcategories of stenoses and were supported by the results for the mean minimal luminal diameter.
Blankernhorn et al.[63] (1987) Colestipol 30 g/day plus niacin 3 to 12 g/day vs placebo	DB, PC, RCT Nonsmoking men 49 to 59 years of age with progressive atherosclerosis who had coronary bypass surgery not involving valve replacement performed ≥3 months prior and a fasting blood cholesterol level 185 to 350 mg/dL	N=188 2 years	Primary: Coronary global change score Secondary: Change from baseline in lipid parameters	Primary: Deterioration in overall coronary status was significantly less with combination therapy compared to placebo (P<0.001). Atherosclerosis regression, as indicated by perceptible improvement in overall coronary status, occurred in 16.2 and 2.4% of patients receiving combination therapy and placebo (P=0.002). Combination therapy resulted in a significant reduction in the average number of lesions per patient that progressed (P<0.03) and the percentage of patients with new atheroma formation in native coronary arteries (P<0.03). The percentage of patients receiving combination therapy with new lesions (P<0.04) or any adverse change in bypass grafts (P<0.03) was significant reduced. Secondary: Large, significant decreases in TC (26 vs 4%), TG (22 vs 5%), LDL-C (43 vs 5%) and LDL-C/HDL-C (57 vs 6%), and a large, significant increase in HDL-C (37 vs 2%) were achieved with combination therapy compared to placebo (P<0.001 for all). Modifications in lipid parameters achieved with combination therapy were significant compared to baseline values (P values not reported).
Brown et al.[64]	DB, RCT	N=120	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1990) Colestipol 5 to 10 g TID plus niacin 125 mg BID titrated to 1 to 1.5 g TID vs Colestipol 5 to 10 g TID plus lovastatin 20 mg BID titrated to 40 mg BID vs placebo (or colestipol if LDL-C was elevated)	Men ≤62 years of age with elevated apo B and a family history of CAD	32 months	Average change in the percent stenosis for the worst lesion in each of the nine proximal segments Secondary: Average changes in all lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	On average, placebo (conventional therapy) increased the index of stenosis by 2.1 percentage points a baseline of 34%. By contrast, it decreased by 0.7 percentage points with colestipol plus lovastatin and by 0.9 percentage points with colestipol and niacin (P<0.003 for trend). At trial end, on average, these nine lesions were almost 3 percentage points less severe among patients treated intensively compared to conventionally. This difference represents almost 1/10 of the amount of disease present at baseline (34% stenosis). Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease when looking at the effect of treatment on certain subsets of lesions (all lesions measured in each patient, lesions causing severe or mild stenosis and those that did not cause total occlusion at baseline). The results with both treatment groups were significantly difference from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.
Eritsland et al.[65] (1996) Omega-3 acid ethyl esters (Omacor®*) 4 g/day vs dietary therapy	RCT Patients admitted for coronary artery bypass grafting without concomitant cardiac surgery	N=610 1 year	Primary: Graft occlusion Secondary: Not reported	Primary: After one year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving omega-3 acid ethyl esters compared to 33% in the control group (OR, 0.77, 95% CI, 0.60 to 0.99; P=0.034). In the omega-3 acid ethyl esters group, 43% of the patients had 21 vein grafts occluded compared to 51% of the patients in the control group (OR, 0.72, 95% CI, 0.51 to 1.01; P=0.05). Secondary: Not reported
Johansen et al.[66] (1999) Omega-3 acid	DB, PC, RCT Patients who were scheduled for elective	N=500 6 months	Primary: Restenosis Secondary:	Primary: Restenosis occurred in 40.6% of the treated stenoses in the omega-3 acid ethyl esters group and in 35.4% of the treated stenoses in the placebo group (OR, 1.25; 95% CI, 0.87 to 1.80; P=0.21).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ethyl esters (Omacor*) 3 g BID vs placebo	coronary angioplasty for one or more lesions in native coronary arteries who had not undergone prior angioplasty		Not reported	One or more restenoses occurred in 45.9% of patients treated with omega-3 acid ethyl esters compared to 44.8% of patients receiving placebo (OR, 1.05; 95% CI 0.69 to 1.59; P=0.82). Secondary: Not reported
Nilsen et al.[67] (2001) Omega-3 acid ethyl esters (Omacor*) 3 g BID vs placebo	PC, RCT Patients >18 years of age with acute MI	N=300 Up to 2 years	Primary: Cardiac events and revascularizations Secondary: Not reported	Primary: Of the patients receiving omega-3 acid ethyl esters, 28% experienced at least one cardiac event compared to 24% of patients in the placebo group (P=0.74). There was no significant difference between the groups with regards to the number, type, or severity of cardiac events. There was no significant difference in the number of revascularizations with omega-3 acid ethyl esters or placebo (HR, 0.92; 95% CI 0.61 to 1.38). Secondary: Not reported
GISSI-Prevenzione Investigators[68] (1999) Omega-3 acid ethyl esters 1 g/day vs vitamin E 300 mg/day vs omega-3 acid ethyl esters 1 g/day vitamin E 300	MC, OL, RCT Patients surviving a recent (≤3 months) MI	N=11,324 3.5 years	Primary: Cumulative rate of all-cause death, nonfatal MI and nonfatal stroke; cumulative rate of cardiovascular death, nonfatal MI, nonfatal stroke Secondary: Analyses of components of primary end points and main causes of death, adverse events	Primary: Treatment with omega-3 PUFA, but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI and nonfatal stroke (RR, 10%; 95% CI, 1 to 18; P=0.048 by 2-way analysis and RR, 15%; 95% CI, 2 to 26; P=0.023 by 4-way analysis). Treatment with omega-3 PUFA decreased the risk of the composite of cardiovascular death, nonfatal MI and nonfatal stroke (RR, 11%; 95% CI, 1 to 20; P=0.053 by 2-way analysis and RR, 20%; 95% CI, 5 to 32; P=0.008 by 4-way analysis). The effect of the combined treatment with omega-3 PUFA and vitamin E was similar to that for omega-3 PUFA for the primary end point (RR, 14%; 95% CI, 1 to 26) and for fatal events (RR, 20%; 95% CI, 5 to 33). Secondary: Analyses of the individual components of the main end point showed that the decrease in mortality (20% for total deaths [P value not reported], 30%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs no treatment				for cardiovascular deaths [P=0.0242] and 45% for sudden deaths [P=0.010]) which was obtained with omega-3 PUFA accounted for all of the benefit seen in the combined end point. There was no difference across the treatment groups for nonfatal cardiovascular events. At one year and at the end of the trial, 11.6 and 28.5% of patients receiving omega-3 PUFA and 7.3 and 26.2% of those receiving vitamin E, respectively, had permanently stopped taking the study drug. Side effects were reported as a reason for discontinuing therapy for 3.8% of patients in the omega-3 PUFA groups and 2.1% of those in the vitamin E groups. Overall, gastrointestinal disturbances and nausea were the most frequently reported side effects (4.9 and 1.4% with omega-3 PUFA and 2.9 and 0.4% with vitamin E, respectively; P values not reported.).

*Omacor was renamed to Lovaza in August 2007.
Drug regimen abbreviations: BID=twice daily, ER=extended-release, IR=immediate release, QD=once daily, SR=sustained release, TID=three times daily
Study abbreviations: DB=double-blind, ES=extension study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, XO=crossover
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo=apolipoprotein, AST=aspartate aminotransferase, BMI=body mass index, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CI=confidence interval, CIMT=carotid intima-media thickness, CPK=creatinine phosphokinase, CRP=C-reactive protein, CV=cardiovascular, DHA=docosahexaenoic acid, EPA=eicosapentaenoic acid, FBG=fasting blood glucose, HAART=high active antiretroviral therapy, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein cholesterol, HIV=human immunodeficiency virus, HOMA-IR=homeostasis model assessment-insulin resistance, HR=hazard ratio, hsCRP=high sensitivity C reactive protein, LDL-C=low-density lipoprotein cholesterol, Lp(a)=lipoprotein(a), MI=myocardial infarction, NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, OR=odds ratio, PCI=percutaneous coronary intervention, PUFA=polyunsaturated fatty acids, RLP-C=remnant like particle cholesterol, RR=relative risk, TC=total cholesterol, TG=triglycerides, VLDL-C=very low-density lipoprotein cholesterol

Additional Evidence

<u>Dose Simplification</u>
A search of Medline and PubMed did not reveal data pertinent to this topic.

<u>Stable Therapy</u>
A search of Medline and PubMed did not reveal data pertinent to this topic.

<u>Impact on Physician Visits</u>
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Antilipemic Agents, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Niacin	extended-release capsule*, extended-release tablet*, tablet*	Niacor®, Niaspan®	$$$$	$
Omega-3 acid ethyl esters	capsule	Lovaza®	$$$$	N/A

*Product is available over-the-counter.
N/A=Not available.

X. Conclusions

Prescription niacin and omega-3 acid ethyl esters are approved by the Food and Drug Administration (FDA) for the treatment of hypertriglyceridemia. Prescription niacin is also approved for the treatment of primary hypercholesterolemia and mixed dyslipidemia.[8,18,19] Niacin is available over-the-counter (OTC) in immediate-release and sustained-release formulations, which are currently on the Alabama Medicaid Preferred Drug List. Niacin is also available by prescription as immediate-release (Niacor®) and extended-release (Niaspan®) formulations. Omega-3 acid ethyl esters (Lovaza®) is only available by prescription. There are no generic formulations currently available for prescription niacin or omega-3 acid ethyl esters.

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended. However, in general, the statins are considered first line therapy for decreasing LDL-C levels, and are recommended in patients with established coronary heart disease (CHD) or CHD equivalents. If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant, niacin, or ezetimibe should be considered. Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy. In patients with an elevated triglyceride level (≥500 mg/dL) a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis. Omega-3-acid ethyl esters represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia. More recent clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease. For all patients, it may be reasonable to recommend omega-3-acid ethyl esters for cardiovascular disease risk reduction.[1,6,7,12-16]

Niacin is the most effective agent for modifying all of the lipid abnormalities associated with atherogenic dyslipidemia, and it is the most effective agent for raising HDL-C.[1] Clinical trials have demonstrated that niacin positively impacts a variety of lipid/lipoprotein parameters.[21-38] Niacin has been shown to reduce the risk of recurrent nonfatal myocardial infarction in patients with hypercholesterolemia, as well as slow the progression or promote regression of atherosclerotic disease (in combination with bile acid sequestrants) in patients with a history of coronary artery disease and hypercholesterolemia.[55,56,62] There are limited head-to-head studies comparing the efficacy and safety of the different niacin formulations.[27-29] While flushing may be more common with the immediate-release formulation, it still occurs with the sustained-release and extended-release products. Cases of severe hepatic toxicity have occurred in patients who have substituted sustained-release niacin products for immediate-release niacin at equivalent doses.[18,19] Due to significant safety concerns, the American Heart Association stresses that dietary supplement niacin must not be used as a substitute for prescription niacin, and should not be used for cholesterol lowering due to the potential for very serious side effects.[11]

Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower triglycerides, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.[39-54] The GISSI-Prevenzione trial demonstrated the beneficial effects of omega-3 acid ethyl esters in patients who have experienced a recent myocardial infarction; omega-3 acid ethyl esters significantly reduced the risk of death, nonfatal myocardial infarction, and nonfatal stroke compared to vitamin E.[68]

Therefore, prescription niacin products (Niacor® and Niaspan®) offer significant clinical advantages in general use over the other brands, generics and OTC niacin products in the same class (if applicable), but are comparable to each other. Due to its limited FDA-approved indications, prescription omega-3 acid ethyl esters should be available through the medical justification portion of the prior authorization process for adults with severe hypertriglyceridemia (≥500 mg/dL).

XI. Recommendations

Prescription niacin is recommended for preferred status. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand prescription niacin product is selected as a preferred agent.

No brand omega-3 acid ethyl ester is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Nitrates and Nitrites
AHFS Class 241208
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I. Overview

Angina occurs when myocardial oxygen demand exceeds supply, which results in chest discomfort or pain. Common treatments for chronic angina include nitrates, β-blockers, and calcium channel blockers.[1] The nitrites and nitrates reduce oxygen demand by decreasing left ventricular pressure and systemic vascular resistance, as well as by dilating coronary arteries.[2-12] β-blockers reduce heart rate and contractility by competitively blocking the response to beta-adrenergic stimulation in the heart. Calcium channel blockers increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction and reducing contractility. They also decrease oxygen demand by reducing systemic vascular resistance and arterial pressure.[13,14]

Tolerance develops after chronic exposure to nitrates, regardless of the route of administration or formulation used. This can be overcome by instituting short periods (10 to 12 hours) of withdrawal from nitrate therapy.[2-14] For example: administer the last dose of a short-acting product prior to 7:00 p.m., administer products twice daily instead of four times daily, or use sustained-release products once daily in the morning.[13,14]

The nitrates and nitrites that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in August 2010.

Table 1. Nitrates and Nitrites Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Isosorbide dinitrate	extended-release capsule, extended-release tablet, sublingual tablet, tablet	Dilatrate-SR®, Isordil®*, Isordil Titradose®*	isosorbide dinitrate
Isosorbide mononitrate	extended-release tablet, tablet	Imdur®*, Monoket®*	isosorbide mononitrate
Nitroglycerin	injection, ointment, sublingual tablet, transdermal patch, translingual spray	Minitran®*, Nitro-Bid®, Nitro-Dur®*, Nitrolingual®*, Nitrostat®, Nitromist®	nitroglycerin§, Nitro-Bid®

*Generic is available in at least one dosage form or strength.
§Covered generic sublingual nitroglycerin tablets are not FDA-approved and are no longer available.[15]
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the nitrates and nitrites are summarized in Table 2.

Table 2. Treatment Guidelines Using the Nitrates and Nitrites

Clinical Guideline	Recommendation(s)
Institute for Clinical Systems Improvement: **Stable Coronary Artery Disease[16] (2011)**	• The use of one aspirin tablet daily (81 to 162 mg) is strongly recommended unless there are medical contraindications. • In patients with mild, stable coronary artery disease (CAD), drug therapy may be limited to short-acting sublingual nitrates on an as-needed basis. • β-blockers should be used in all status post-myocardial infarction (MI)

Clinical Guideline	Recommendation(s)
	patients, based on studies showing mortality reduction. • β-blockers are the preferred first-line therapy for reducing symptoms of angina in patients with stable CAD. • Drugs with intrinsic sympathomimetic activity should be avoided. • Abrupt withdrawal of all β-blockers should be avoided. • If β-blockers cannot be prescribed as first-line therapy, nitrates are the preferred alternative first-line therapy because of efficacy, low cost, and relatively few adverse events. • For patients who are unable to take β-blockers or long-acting nitrates, the use of calcium channel blockers has been shown to be clinically effective in decreasing symptoms of angina. Dihydropyridines as monotherapy may exacerbate angina. • Combination therapy may be necessary in selected patients, but it increases adverse events and medical costs. A combination of β-blockers and long-acting nitrates is preferred because of cost, efficacy, and reduced potential for adverse events. • If after several attempts at adjusting the medications, a therapeutic combination is not achieved for the patient, a cardiology consultation or referral may be appropriate. • Among patients with stable angina, angiotensin converting enzyme (ACE) inhibitors are most beneficial to patients with left ventricular dysfunction post-MI, persistent hypertension, and diabetes. If the patient cannot tolerate ACE inhibitors, a potential substitute would be an angiotensin II receptor blocker (ARB). • The decision to initiate daily drug therapy for CAD is based upon the symptom complex of the patient in combination with findings from the history, physical examination, laboratory studies and prognostic testing. • Ranolazine is not a first-line drug and should be used in conjunction with a cardiologist.
American College of Cardiology /American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina[17] (2007)**	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. • Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. • Patients with hypertension and established CAD should be treated with blood pressure medication(s) as tolerated, including ACE inhibitors and/or β-blockers with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. • Long-acting calcium channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. • ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. • ARBs are recommended in patients with hypertension, those who have

Clinical Guideline	Recommendation(s)
	an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction and have a LVEF of ≤40%. • ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. • Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • Annual influenza vaccination is recommended in patients with cardiovascular disease.
American College of Cardiology/American Heart Association: **2002 Guideline Update for the Management of Patients With Chronic Stable Angina[18] (2002)**	• Aspirin 75 to 325 mg should be used routinely in all patients with acute and chronic ischemic heart disease unless contraindicated. Clopidogrel may be used when aspirin is contraindicated. • β-blockers should be considered as initial therapy for chronic stable angina. • HMG-CoA reductase inhibitors should be recommended even in mild-to-moderate elevations of low-density lipoprotein cholesterol. • ACE inhibitors should be prescribed to patients with diabetes and/or left ventricular systolic dysfunction. • There is insufficient evidence for using an angiotensin receptor blocker in chronic stable angina. • Use sublingual nitroglycerin (NTG) or NTG spray for immediate relief of angina. • Long-acting calcium channel blockers or long-acting nitrates may be used if β-blockers are contraindicated. • An immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. • A long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful.
European Society of Cardiology: **Management of Stable Angina Pectoris[19] (2006)**	<u>Therapy to improve prognosis</u> • Aspirin 75 mg once daily is recommended in all patients without contraindications. • Statin therapy is recommended for all patients with coronary disease. • ACE inhibitor therapy is recommended for patients with indications for ACE inhibition including hypertension, heart failure, left ventricular dysfunction and history of myocardial infarction with left ventricular dysfunction and diabetes. • β-blocker therapy is recommended in patients with history of myocardial infarction or heart failure. • Class IIa evidence includes ACE inhibition in patients with angina and proven coronary disease, clopidogrel in patients with stable angina who are not candidates for aspirin and high dose statin therapy in high risk patients with proven coronary disease. • Class IIb evidence includes fibrates in patients with low high density lipoprotein cholesterol and high triglycerides who have diabetes or metabolic syndrome. • Calcium channel blockers may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial infarction and who do not have heart failure.

Clinical Guideline	Recommendation(s)
	Therapy to improve symptoms and/or reduce ischemia • Short-acting NTG therapy is recommended for acute symptom relief and situational prophylaxis. • Test the effects of a β1 blocker and titrate to full dose; consider the need for 24-hour protection against ischemia. • If β-blockers are not effective or not tolerated, attempt monotherapy with a calcium channel blocker, long-acting nitrate or nicorandil*. • If the effects of β-blocker therapy are insufficient, add a dihydropyridine calcium channel blocker. • Class IIa evidence includes a sinus node inhibitor in the case of β-blocker intolerance, or a long-acting nitrate or nicorandil* in place of a calcium channel blocker in the case of insufficient response to calcium channel blocker monotherapy or combination therapy with a calcium channel blocker and β-blocker. • Class IIb evidence includes the use of metabolic agents where available as add-on therapy or in place of conventional therapy when conventional therapy is not tolerated. Treatment of syndrome X • Therapy with nitrates, β-blockers and calcium channel blockers alone or in combination is recommended. • Statin therapy is recommended in patients with hyperlipidemia. • ACE inhibitors are recommended in patients with hypertension. • Class IIa evidence includes a trial of other anti-anginal agents such as nicorandil and metabolic agents. Treatment of vasospastic angina • Treatment with calcium channel blockers is recommended in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.
American College of Physicians: **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known Coronary Artery Disease**[20] **(2004)**	• β-blockers should be strongly considered as initial therapy, unless contraindicated. • ACE inhibitors should be recommended for patients with symptomatic chronic stable angina to prevent myocardial infarction and death and to reduce symptoms of angina, and in patients with asymptomatic chronic stable angina with coronary artery disease, who also have diabetes mellitus, systolic dysfunction, or both. • Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful or if β-blockers are contraindicated. • Sublingual NTG or NTG spray for immediate symptomatic relief of angina.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation**[21] **(2012)**	Long-term therapies for ST-segment elevation myocardial infarction (STEMI)-nitrates • The routine use of nitrates in STEMI has not been shown to be of value; therefore, is not recommended. • Intravenous nitrates may be useful during the acute phase in patients with hypertension or heart failure, with no hypotension, right ventricular infarction, or use of phosphodiesterase type 5 inhibitors in the previous 48 hours. • In the acute and stable phase, nitrates remain valuable to control symptoms of angina.
American College of Cardiology/American Heart	Immediate management • Low-risk patients that are referred to outpatient stress testing should be

Clinical Guideline	Recommendation(s)
Association Task Force on Practice Guidelines: **2007 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-segment Elevation Myocardial Infarction (2007)**[22]	given medications such as sublingual NTG, aspirin and/or β-blockers as a preventative measure. <u>Early hospital care-recommendations for anti-ischemic therapy</u> • Patients with unstable angina/non-ST-segment myocardial infarction (NSTEMI) with ongoing ischemic discomfort should receive sublingual NTG every five minutes for a total of three doses, after which assessment should be about the need for intravenous NTG. Intravenous NTG is indicated in the first 48 hours after unstable angina/NSTEMI for treatment of persistent ischemic, heart failure, or hypertension. • Oral β-blocker therapy should be initiated within the first 24 hours for patients who do not have one or more of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk for cardiogenic shock, or 4) other relative contraindications to β blockade. • In unstable angina/NSTEMI patients with continuing or frequently recurring ischemia and in whom β-blockers are contraindicated, a nondihydropyridine calcium channel blocker should be given as initial therapy in the absence of clinically significant left ventricular dysfunction or other contraindications. • Oral long-acting nondihydropyridine calcium channel blockers are reasonable for use in unstable angina/NSTEMI patients for recurrent ischemic in the absence of contraindications after β-blockers and nitrates have been fully used. • Use of extended-release forms of nondihydropyridine calcium channel blockers instead of a β-blocker may be considered in patients with unstable angina/NSTEMI. Immediate-release dihydropyridine calcium channel blockers in the presence of adequate β-blockade may be considered in patients with unstable angina/NSTEMI with ongoing ischemic symptoms or hypertension. • An ACE inhibitor should be administered orally within the first 24 hours to unstable angina/NSTEMI patients with pulmonary congestion or LVEF ≤40%, in the absence of hypotension or known contraindications. An ARB should be administered in patients who are intolerant to ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF ≤40%. • An oral ACE inhibitor administered within the first 24 hours of unstable angina/NSTEMI can be useful in patients without pulmonary congestion or LVEF ≤40% in the absence of hypotension or known contraindications. • Ranolazine may be safely administered for symptom relief after unstable angina/NSTEMI, but it does not appear to significantly improve the underlying disease substrate. <u>Late hospital care, hospital discharge, and post-hospital discharge care</u> • All post-unstable angina/NSTEMI patients should be given sublingual or spray NTG and instructed in its use. • β-blockers are indicated for all patients recovering from unstable angina/NSTEMI unless contraindicated. Therapy should be continued indefinitely. • ACE inhibitors should be given and continued indefinitely for patients recovering unstable angina/NSTEMI with heart failure, left ventricular dysfunction, hypertension, or diabetes, unless contraindicated. An ARB should be prescribed at discharge in patients who are intolerant to ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF ≤40%.

Clinical Guideline	Recommendation(s)
	• NTG to treat ischemic symptoms is recommended. • Calcium channel blockers are recommended for ischemic symptoms when β-blockers are not successful. • Calcium channel blockers are recommended for ischemic symptoms when β-blockers are contraindicated or cause unacceptable side effects. Note: A focused update to the 2007 guideline was published in 2012; however, the recommendations above were not updated and remain current to the 2007 guideline. The 2012 focused update focuses on antiplatelet and anticoagulant therapies.[23]
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-segment Elevation[24] (2011)**	Anti-ischemic drugs • Oral or intravenous nitrate treatment is indicated to relieve angina. Intravenous nitrates are recommended in patients with recurrent angina and/or signs of heart failure. • Patients on chronic β-blocker therapy admitted with acute coronary syndrome should be continued on β-blocker therapy if not in Killip class ≥III. • Oral β-blocker therapy is indicated in all patients with left ventricular dysfunction, unless contraindications are present. • Calcium channel blockers are recommended for relief of symptoms in patients already receiving nitrates and β-blocker therapy, and in patients with contraindications to β-blockade. • Calcium channel blockers are recommended in patients with vasospastic angina. • Intravenous β-blocker therapy at the time of admission should be considered for patients with stable hemodynamics with hypertension and/or tachycardia. • Nifedipine, or other dihydropyridines, are not recommended unless combined with β-blockers.
American College of Cardiology/American Heart Association: **Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction-Pharmacological Management[25] (2004)**	Initial emergency department management • Sublingual NTG 0.4 mg should be given to patients with ongoing ischemic discomfort every five minutes for three total doses. After three doses, assess need for intravenous NTG. • Intravenous NTG is indicated for relief of ongoing ischemic discomfort, control of hypertension or management of pulmonary congestion. Hospital management–medication assessment • Intravenous NTG is indicated during the first 48 hours for treatment of persistent ischemia, hypertension or congestive heart failure, provided that therapy does not preclude treatment with β-blockers or ACE inhibitors. • NTG after 48 hours can be useful for recurrent angina or persistent congestive heart failure provided that therapy does not preclude treatment with β-blockers or ACE inhibitors. Note: Focused updates to the 2004 guideline were published in 2007 and 2009; however, the recommendations for the nitrates and nitrites were not updated and remain current to the 2004 guideline.[26,27]
Institute for Clinical Systems Improvement: **Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome[28] (2012)**	Early therapy-NTG • ISIS-4 and GISSI-3 failed to show a benefit of NTG on reduction of mortality in acute MI. • NTG should be given sublingually to relieve ischemic symptoms. If symptoms are ongoing or recurrent despite the administration of intravenous β-blockers, intravenous NTG can be initiated.

Clinical Guideline	Recommendation(s)
	• NTG is contraindicated in patients who are hypotensive, have documented severe aortic stenosis, have hypertrophic cardiomyopathy, or who have received sildenafil or vardenafil within the previous 24 hours or tadalafil in the previous 48 hours. • Consider oral nitrates for outpatients with ongoing angina. • Oral nitrates may benefit selected patients with postinfarction mortality in all MIs.
National Institute for Health and Clinical Excellence: **Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction[29] (2007)**	Patients with prior myocardial infarction without heart failure • Calcium channel blockers, nitrates, and potassium channel activators have no effect on premature mortality and can be used for management of risk factors such as hypertension in patients intolerant to a β-blocker and an ACE inhibitor.
American College of Cardiology/American Heart Association: **Guideline for the Diagnosis and Management of Heart Failure in Adults[30] (2009; Focused Update)**	• The addition of a combination of hydralazine and a nitrate is reasonable for patients with heart failure who are already taking an ACE inhibitor and β-blocker for symptomatic heart failure, but who have persistent symptoms. • A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of heart failure and reduced LVEF who cannot be given an ACE inhibitor or an ARB because of drug intolerance, hypotension, or renal insufficiency. • The combination of hydralazine and nitrates is recommended to improve outcomes for patients self-described as African American, with moderate to severe symptoms on optimal therapy with ACE inhibitors, β-blockers and diuretics. • Combination of fixed-dose hydralazine and isosorbide dinitrate to a standard regimen for heart failure, including ACE inhibitors and β-blockers, is recommended in order to improve outcomes for patients self-described as African American, with New York Heart Association (NYHA) functional class III or IV heart failure. Any potential benefit in other patients has yet to be evaluated. • Patients with heart failure should be given nitrates and β-blockers for the treatment of angina. • Vasodilators (i.e., intravenous NTG, nitroprusside or nesiritide) can be beneficial when added to diuretics and/or in those who do not respond to diuretics alone in patients with severely symptomatic fluid overload in the absence of systemic hypotension.
Institute for Clinical Systems Improvement: **Heart Failure in Adults[31] (2011)**	Pharmacologic management: • Carvedilol, metoprolol succinate (extended-release) and bisoprolol have demonstrated reductions in mortality for patients with all classes of heart failure. These agents should be used before using other generic β-blockers. • ACE inhibitors should be prescribed for all patients with left ventricular systolic dysfunction unless contraindications are present. • If non-African American, ACE inhibitors are recommended for decreasing heart failure mortality than isosorbide dinitrate/hydralazine. In contrast, combination hydralazine and nitrates is recommended for patients self-described as African Americans, with moderate to severe symptoms on optimal therapy with ACE inhibitors, β-blockers, and diuretics. • ARBs should be considered primarily for patients who are intolerant to ACE inhibitors or in patients receiving standard drug therapy (including ACE inhibitors) who continue to show clinical

Clinical Guideline	Recommendation(s)
	deterioration. • Routine use of ARBs and ACE inhibitors and aldosterone antagonists cannot be recommended. • Diuretics should not be the sole therapy for patients with signs of volume overload; vasoactive drugs should be considered. • In severe heart failure, loop diuretics should be used over thiazide diuretics and combination therapy with thiazide. Loop diuretics are also effective in refractory cases of volume overload. • Patients with NYHA class III-IV heart failure on stable doses of digoxin and ACE inhibitors can reduce mortality by administering aldosterone-blocking agents. • Nesiritide is recommended to be reserved for patients with decompensated heart failure who remain volume overloaded despite aggressive treatment with diuretics/vasodilators display tolerance and/or resistance to vasodilators or diuretics, or demonstrate significant side effects to other vasodilators. • When considering the use of calcium channel blockers, only dihydropyridine calcium channel blockers have been shown safe. Non-dihydropyridine calcium channel blockers can be used in patients with preserved systolic heart failure.
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines[32] (2010)**	• Combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE inhibitors for African Americans with heart failure and reduced LVEF. • In patients with reduced LVEF, combination hydralazine and an oral nitrate may be considered when ACE inhibitors are not tolerated due to hyperkalemia or renal insufficiency or ARBs are not tolerated due to cough or angioedema. • May be considered in non–African American patients with left ventricular dysfunction who remain symptomatic despite optimized standard therapy. • Addition of the combination of hydralazine and isosorbide dinitrate should be considered in African American patients with heart failure and reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with ACE inhibitors and β-blocker or unable to tolerate a β-blocker. • In patients admitted with acute decompensated heart failure, intravenous NTG, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in the absence of symptomatic hypotension. • Intravenous vasodilators (NTG or nitroprusside) and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. • Intravenous vasodilators (NTG, nesiritide, or nitroprusside) can be considered in patients with acute decompensated heart failure who have persistent symptoms despite aggressive treatment with diuretics and standard oral therapy. • Nitrates should be considered in patients with heart failure when additional medication is needed for anginal symptoms.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[33] (2012)**	<u>Treatment of acute heart failure</u> • Vasodilators, such as NTG, reduce preload and afterload and increase stroke volume; however, there is no robust evidence that these agents relive dyspnea or improve other clinical outcomes. • Vasodilators are most useful in patients with hypertension and should be avoided in patients with systolic blood pressure <110 mm Hg. • Vasodilators should be used with caution in patients with significant

Clinical Guideline	Recommendation(s)
	mitral or aortic stenosis.
National Institute for Health and Clinical Excellence: **Management of Chronic Heart Failure in Adults in Primary and Secondary Care**[34] **(2003)**	• An isosorbide/hydralazine combination may be used in patients with heart failure who are intolerant to ACE inhibitors or ARB's.
European Society of Cardiology: **Guidelines for Pre-Operative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery**[35] **(2009)**	• NTG has been shown to reverse myocardial ischemia. • Perioperative NTG use for the prevention of adverse ischemic events may be considered
Joint National Committee: **The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure**[36] **(2003)**	• Intravenous NTG, at a rate of 5 to 100 µg/min, is among the treatment options for the management of hypertensive emergencies, particularly in the setting of coronary ischemia. • Intravenous NTG's onset and duration of action are two to five minutes and five to ten minutes, respectively.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the nitrates and nitrites are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Nitrates and Nitrites[2-12]

Indication	Isosorbide Dinitrate*	Isosorbide Mononitrate*	Nitroglycerin		
			Lingual spray/ Sublingual tablet	Injection	Topical/ Transdermal*
Angina Pectoris					
Acute relief of an attack of angina pectoris			✔		
Prevention of angina pectoris due to coronary artery disease	✔	✔	✔		✔
Treatment of angina pectoris due to coronary artery disease	✔ (sublingual tablet)	✔ (tablet)		✔ †	
Cardiovascular Uses					
Control of congestive heart failure in the setting of acute myocardial infarction				✔	
Induction of intraoperative hypotension				✔	
Treatment of perioperative hypertension				✔	

*The onset of action of this product is not sufficiently rapid for it to be useful in aborting an acute attack.
†In patients who have not responded to sublingual nitroglycerin and beta-blockers.

IV. Pharmacokinetics

The pharmacokinetic parameters of the nitrates and nitrites are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Nitrates and Nitrites[14]

Generic Name(s)	Bioavailability (%)	Onset (minutes)	Duration	Excretion (%)	Half-Life
Isosorbide dinitrate	ER: 22 IR: 58 SL: 19 to 93	SL: 2 to 10	IR: 8 hours SL: 1 to 2 hours	Renal (80 to 90) Feces (limited; % not reported)	ER: 4 hours IR: 4 hours SL: 1 hour
Isosorbide mononitrate	ER: 80 to 100 IR: 93 to 100	ER: 45 to 60 IR: 45 to 60	ER: 6 hours IR: 6 hours	Renal (78) Feces (1)	ER: 6 hours IR: 6 hours
Nitroglycerin	Patch: 75* SL: 38.5	Oint: 30 to 60 SL: 1 to 3	Oint: 7 hours Patch: 8 to 10 hours SL: up to 60 minutes	Renal (22)	1.5 to 7.5 minutes

*Compared to intravenous dosing.
ER=extended-release, IR=immediate-release, Oint=ointment, SL=sublingual

V. Drug Interactions

Significant drug interactions with the nitrates and nitrites are listed in Table 5.

Table 5. Significant Drug Interactions with the Nitrates and Nitrites[13]

Generic Name(s)	Significance Level	Interaction	Mechanism
Isosorbide dinitrate, Isosorbide mononitrate, Nitroglycerin	1	Avanafil	Avanafil potentiates the hypotensive effects of nitrates, resulting in severe hypotension.
Isosorbide dinitrate, Isosorbide mononitrate, Nitroglycerin	1	Sildenafil, tadalafil, vardenafil	Sildenafil may potentiate the hypotensive effects of nitrates. The use of these agents in combination is contraindicated.
Nitroglycerin	1	Alteplase	Concentrations of tissue-type plasminogen activator (tPA) are decreased, indicating impairment of the thrombolytic effect of alteplase. The enhanced hepatic blood flow as a result of the nitroglycerin facilitates the hepatic metabolism of tPA.
Isosorbide dinitrate, Isosorbide mononitrate, Nitroglycerin	2	Dihydroergotamine	The metabolism of dihydroergotamine is decreased thus increasing its bioavailability. The dose of the dihydroergotamine may need to be decreased.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the nitrates and nitrites are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Nitrates and Nitrites[2-14]

Adverse Events	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Cardiovascular				

Adverse Events	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Abnormal heart sound	-	≤5	-	-
Aggravated angina pectoris	-	≤5	-	-
Angina pectoris	-	-	≥1	-
Arrhythmia	-	≤5	<1	-
Atrial fibrillation	-	≤5	<1	-
Bradycardia	-	≤5	-	-
Bundle branch block	-	≤5	-	-
Cardiac failure	-	≤5	-	-
Crescendo angina	✔	-	-	✔
Extrasystole	-	≤5	-	-
Flushing	-	≤5	-	✔
Heart murmur	-	≤5	-	-
Hypertension	-	≤5	-	-
Hypotension	✔	≤5	<1	4
Migraine	-	≤5	-	-
Myocardial infarction	-	≤5	✔	-
Palpitation	-	≤5	<1	✔
Postural hypotension	✔	-	<1	✔
Premature ventricular contraction	-	-	<1	-
Q wave abnormality	-	≤5	-	-
Rebound hypertension	✔	-	-	✔
Supraventricular tachycardia	-	-	<1	-
Syncope	✔	✔	<1	✔
Tachyarrhythmia	-	-	-	-
Tachycardia	-	≤5	-	-
Ventricular tachycardia	-	≤5	-	-
Central Nervous System				
Anxiety	-	≤5	<1	-
Confusion	-	≤5	<1	-
Decreased libido	-	≤5	-	-
Depression	-	≤5	-	-
Dizziness	✔	8 to 11	3 to 5	≥2
Headache	✔	≥5	19 to 38	50 to 63
Impotence	-	≤5	<1	-
Insomnia	-	≤5	<1	-
Lightheadedness	✔	-	-	6
Nervousness	-	≤5	<1	-
Neuritis	-	≤5	-	-
Paresis	-	≤5	-	-
Paresthesia	-	≤5	-	≥2
Purpura	-	≤5	-	-
Somnolence	-	≤5	-	-
Vertigo	-	≤5	-	✔
Dermatological				
Acne	-	≤5	-	-
Anaphylactoid reactions	-	-	-	✔
Contact dermatitis	-	-	-	✔ *
Exfoliative dermatitis	-	-	-	✔
Photophobia	-	≤5	-	-
Pruritus	-	≤5	<1	-
Rash	-	≤5	<1	✔
Skin nodule	-	≤5	-	-
Gastrointestinal				

Adverse Events	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Abdominal pain	-	≤5	<1	≤2
Constipation	-	≤5	-	-
Diarrhea	-	≤5	<1	-
Dyspepsia	-	≤5	<1	-
Flatulence	-	≤5	-	-
Gastric ulcer	-	≤5	-	-
Gastritis	-	≤5	-	-
Hemorrhagic gastric ulcer	-	≤5	-	-
Loose stools	-	≤5	-	-
Nausea	-	≤5	2 to 4	✔
Vomiting	-	≤5	2 to 4	✔
Genitourinary				
Dysuria	-	-	<1	-
Polyuria	-	≤5	-	-
Renal calculus	-	≤5	-	-
Urinary tract infection	-	≤5	-	-
Hematologic				
Hemolytic anemia	-	-	-	-
Hypochromic anemia	-	≤5	-	-
Methemoglobinemia	✔	✔	✔	✔
Thrombocytopenia	-	≤5	-	-
Laboratory Test Abnormalities				
Elevated SGOT	-	≤5	-	-
Elevated SGPT	-	≤5	-	-
Musculoskeletal				
Arthralgia	-	≤5	<1	-
Asthenia	-	≤5	<1	-
Muscle weakness	-	≤5	-	-
Musculoskeletal pain	-	≤5	-	-
Myalgia	-	≤5	-	-
Respiratory				
Bronchitis	-	≤5	<1	-
Bronchospasm	-	≤5	-	-
Coughing	-	≤5	-	-
Dyspnea	-	≤5	-	≤2
Increased sputum	-	≤5	-	-
Nasal congestion	-	≤5	-	-
Pharyngitis	-	≤5	-	-
Pneumonia	-	≤5	<1	-
Pulmonary infiltration	-	≤5	-	-
Rales	-	≤5	-	-
Rhinitis	-	≤5	-	-
Sinusitis	-	≤5	-	-
Upper respiratory tract infection	-	-	<1	-
Other				
Abnormal hair texture	-	≤5	-	-
Abnormal vision	-	≤5	-	-
Agitation	-	-	<1	-
Atrophic vaginitis	-	≤5	-	-
Back pain	-	≤5	-	-
Bacterial infection	-	≤5	-	-
Blurred vision	✔	-	<1	-
Breast pain	-	≤5	-	-

Adverse Events	Isosorbide Dinitrate	Isosorbide Mononitrate SR	Isosorbide Mononitrate IR	Nitroglycerin
Chest pain	-	≤5	-	-
Cold sweat	-	-	<1	-
Collapse	-	-	-	✔
Conjunctivitis	-	≤5	-	-
Diplopia	-	-	<1	-
Dry mouth	-	≤5	-	-
Discoordination	-	-	<1	-
Earache	-	≤5	-	-
Edema	-	≤5	<1	-
Fatigue	-	≤5	-	-
Fever	-	≤5	-	-
Flu-like symptoms	-	≤5	-	-
Frozen shoulder	-	≤5	-	-
Glossitis	-	≤5	-	-
Hemorrhoids	-	≤5	-	-
Hot flashes	-	≤5	-	-
Hyperuricemia	-	≤5	-	-
Hypoesthesia	-	≤5	<1	-
Hypokalemia	-	≤5	-	-
Hypokinesia	-	-	<1	-
Impaired concentration	-	≤5	-	-
Increased appetite	-	-	<1	-
Increased sweating	-	≤5	-	-
Intermittent claudication	-	≤5	-	-
Leg ulcer	-	≤5	-	-
Malaise	-	≤5	<1	-
Melena	-	≤5	-	-
Moniliasis	-	≤5	-	-
Myositis	-	≤5	-	-
Nightmares	-	-	<1	-
Pallor	-	-	-	✔
Paroniria	-	≤5	-	-
Ptosis	-	≤5	-	-
Restlessness	-	-	-	✔
Rigors	-	≤5	<1	-
Tendon disorder	-	≤5	-	-
Tenesmus	-	-	<1	-
Tinnitus	-	≤5	-	-
Tooth disorder	-	-	<1	-
Tremor	-	≤5	-	-
Tympanic membrane perforation	-	≤5	-	-
Varicose veins	-	≤5	-	-
Viral infection	-	≤5	-	-
Weakness	-	-	-	✔

IR=immediate-release, SR=sustained-release
*Topical formulation only.
✔ Percent not specified.
- Event not reported.

VII. Dosing and Administration

The usual dosing regimens for the nitrates and nitrites are listed in Table 7.

Table 7. Usual Dosing Regimens for the Nitrates and Nitrites[2-12]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Isosorbide dinitrate	Angina pectoris: Extended-release capsule, extended-release tablet: initial, 40 mg/day; maintenance, 40 to 80 mg every 8 to 12 hours; maximum, 160 mg/day Sublingual tablet (treatment): initial, 2.5 to 5 mg; maintenance, titrate upward until angina is relieved or side effects limit the dose Sublingual tablet (prophylaxis): 2.5 to 5 mg approximately 15 minutes before the anticipated activity likely to cause angina is expected to begin* Tablet: initial, 5 to 20 mg two or three times daily; maintenance, 10 to 40 mg two or three times daily	Safety and efficacy in children have not been established.	Extended-release capsule: 40 mg Extended-release tablet: 40 mg Sublingual tablet: 2.5 mg 5 mg Tablet: 5 mg 10 mg 20 mg 30 mg 40 mg
Isosorbide mononitrate	Angina pectoris: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, dosage may be increased to 120 mg once daily, 240 mg/day may be required Tablet: initial, 5 to 10 mg/day; maintenance, 20 mg twice daily, with the two doses administered seven hours apart	Safety and efficacy in children have not been established.	Extended-release tablet: 30 mg 60 mg 120 mg Tablet: 10 mg 20 mg
Nitroglycerin	Angina pectoris: Injection, ointment, sublingual tablet, transdermal patch, translingual spray: there is no fixed optimum dose Injection: 5 µg/min; increase 5 µg/min every 3 to 5 minutes until some response is noted; if no response at 20 µg/min, increase by 10 µg/min every 3 to 5 minutes, up to 200 µg/min; maximum, 400 µg/mL Ointment: ½ inch (1.3 cm, 7.5 mg) to 2 inches (5.1 cm, 30 mg) typically applied to 36 square inches of truncal skin	Safety and efficacy in children have not been established.	Injection: 0.1 mg/mL 0.2 mg/mL 0.4 mg/mL 5 mg/mL Ointment: 2% Sublingual tablet: 0.3 mg 0.4 mg 0.6 mg Transdermal patch: 0.1 mg/hr 0.2 mg/hr 0.3 mg/hr 0.4 mg/hr

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Sublingual tablet: 1 tablet dissolved under the tongue or in the buccal pouch at the first sing of an acute attack; maintenance, the dose may be repeated approximately every 5 minutes until relief is obtained; maximum, 3 tablets within a 15 minute period Transdermal patch: initial, 0.2 and 0.4 mg/hr; maintenance, 0.4 and 0.8 mg/hr; the appropriate dosing schedule would include a daily patch-on period of 12 to 14 hours and a daily patch-off period of 10 to 12 hours Translingual spray: 1 or 2 metered sprays administered onto or under the tongue at the onset of an attack; maximum, no more than 2 sprays are recommended within a 15 minute period <u>Congestive heart failure:</u> Injection: 5 µg/min; increase 5 µg/min every 3 to 5 minutes until some response is noted; if no response at 20 µg/min, increase by 10 µg/min every 3 to 5 minutes, up to 200 µg/min; maximum, 400 µg/mL <u>Intraoperative hypotension and perioperative hypertension:</u> Injection: 5 µg/min; increase 5 µg/min every 3 to 5 minutes until some response is noted; if no response at 20 µg/min, increase by 10 µg/min every 3 to 5 minutes, up to 200 µg/min; maximum, 400 µg/mL		0.6 mg/hr 0.8 mg/hr Translingual spray: 0.4 mg/dose

*Isosorbide dinitrate sublingual tablet may be used to abort an acute anginal episode, but its use is recommended only in patients who fail to respond to sublingual nitroglycerin.

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the nitrates and nitrites are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Nitrates and Nitrites

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chronic Stable Angina				
Parker et al.[37] (1993) ISMN 5 mg BID vs ISMN 10 mg BID vs ISMN 20 mg BID vs placebo	DB, PC, PG Patients with stable angina underwent testing prior to exercise as well as 2 and 7 hours after each dose on days 1 and 14. Additionally, on days 7 and 21, testing was performed 2 hours after the first dose.	N=214 3 weeks	Primary: Total exercise duration and time to moderate angina Secondary: Not reported	Primary: ISMN, at all doses, showed improvement over placebo at 2 and 7 hours after the morning dose and 2 hours after the second dose on day 1. Active treatment prolonged exercise duration over placebo at 2 hours postdose for each of the 2 daily doses. ISMN 20 mg was the only strength which demonstrated increased exercise duration 7 hours after administration, which occurred on day 14. Overall, there were fewer episodes of angina noted in the ISMN 20 mg group. Secondary: Not reported
Thadani et al.[38] (1994) ISMN 20 mg BID vs placebo Patients were allowed to continue β-blocker therapy.	DB, MC, PC, PG, RCT Patients with stable exertional angina who stopped treadmill exercise secondary to angina pectoris	N=116 2 weeks	Primary: Total exercise duration (time to moderately severe angina) Secondary: ST-segment depression, heart rate, DBP and SBP, number of anginal attacks, number of nitroglycerin doses	Primary: A statistically significant improvement in total exercise duration was observed at both the morning and afternoon dose compared to placebo (P<0.01). Secondary: The magnitude of ST-segment depression was comparable in both the isosorbide-5-mononitrate and placebo groups (1.2±0.1 vs 1.2±0.2 mm; P>0.2). Heart rate and SBP, during the period of exercise, was determined to be similar among the groups. Additionally, the number of anginal attacks and doses of nitroglycerin were no different per group.
Chrysant et al.[39]	DB, RCT	N=313	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1993) ISMN ER 30 mg in the morning vs ISMN ER 60 mg in the morning vs ISMN ER 120 mg in the morning vs ISMN ER 240 mg in the morning vs placebo	Patients with stable effort-induced angina	6 weeks	Mean change from baseline in total exercise time (serial exercise testing immediately prior to and four and two hours after administration, on days one, seven, 14, 28 and 42) Secondary: Adverse effect	A significant improvement in mean total exercise time of 30 to 50 seconds was shown in all active-treatment groups compared to placebo at 4 and 12 hours postdose (P<0.01). The mean changes from baseline in total exercise time in patients on ISMN ER 120 mg or 240 mg surpassed placebo by about 50 to 60 seconds at 4 hours postdose (P<0.01), and by 30 to 35 seconds 12 hours after dosing (P≤0.05). There was no meaningful difference in response found between active treatment and placebo at 24 hours after administration, thus no indication that ISMN ER induced rebound angina. Secondary: The most common adverse effect among active treatment groups was transient headache.
Bray et al.[40] (1991) NTG administered buccally vs NTG administered sublingually	DB, MC Patients with proven chronic stable exercise-induced angina	N=Not reported Duration not reported	Primary: Efficacy Secondary: Not reported	Primary: The two formulations had comparable effects on acute attacks of angina pectoris. Secondary: Not reported
Ryden et al.[41] (1987) NTG administered	MC, XO Patients with stable angina pectoris	N=126 2 weeks	Primary: Efficacy Secondary:	Primary: Buccal NTG resulted in 31% less acute anginal attacks compared to the sublingual formulation (P<0.001). Prophylaxis was effective in 74% of patients taking buccal NTG compared to 66% of sublingual-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
buccally vs NTG administered sublingually			Ease of use, patient preference	patients (P<0.05). Secondary: There was no difference in ease of use reported in 67% of patients, whereas 19% indicated that sublingual NTG was easier and 14% buccal NTG. Overall, 65% of patients preferred buccal NTG and 19% preferred sublingual NTG (P<0.05). As far as prophylactic use, buccal administration was again preferred by more patients (81%) than sublingual use (4%; P<0.05).
Demots et al.[42] (1989) NTG 0.2 mg/hour or 0.4 mg/hour transdermal patch for 12 hours (Group A) vs NTG 0.6 mg/hour or 0.8mg/hour transdermal patch for 12 hours (Group B) vs placebo	DB, RCT Patients with chronic stable angina	N=206 4 weeks	Primary: Effectiveness in chronic stable angina (serial treadmill testing performed 0, four, eight and 12 hours after patch application at baseline and on days one, 15 and 29) Secondary: Adverse reaction	Primary: Improved walking times were observed in both Group A and Group B over placebo at all testing points after short-term administration. Results were statistically significant for Group A at 12 hours and for Group B at four, eight and 12 hours. At weeks two and four, walking times were again greater in Group B over placebo at all testing points with the four hour test time at week two and the eight hour test time at week two and four reaching statistical significance. Group A did not demonstrate increased duration in walking time long-term. Secondary: Active therapy was generally tolerated well. An increase in nonexertional angina during the patch-off interval was reported in nine patients.
Ninomiya et al.[43] (2008) ISDN ER 40 mg/day or ISMN ER 40 mg/day vs	RCT Patients suspected to have angina pectoris and with normal or mildly diseased coronary arteries underwent	N=42 Not specified	Primary: Coronary wall shear stress Secondary: Changes in coronary blood flow	Primary: The percent increase in coronary blood flow and coronary artery diameter induced by acetylcholine was significantly smaller in the ISDN/ISMN group than in the calcium channel blocker group (33±74 vs 83±77%; P<0.05, -3±16 vs 11±12%; P<0.01, respectively). Secondary: The percent diameter decrease in the region of greatest constrictive

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amlodipine 5mg/day or nifedipine ER 20 mg/day	Doppler flow study of the left anterior descending coronary artery. All patients had been taking long acting nitrates or calcium channel blockers for ≥1 year			response to acetylcholine was significantly greater in the ISDN/ISMN group than in the calcium channel blocker group (44±39 vs 15±32%; P<0.02).
Unstable Angina				
Dellborg et al.[44] (1991) NTG IV for 24 hours vs NTG administered buccally every 4 hours	RCT Patients admitted to the coronary care unit due to UA	N=29 24 hours	Primary: Efficacy Secondary: Adverse effects	Primary: Efficacy was comparable in the two groups Secondary: Less adverse effects (headache, hemodynamic intolerance) were associated with buccal nitroglycerin than IV although the differences were not significant.
Kaplan et al.[45] (1983) NTG IV 10 µg/min increased by 10 µg/min every 5 minutes to 50 µg/min then increased by 50 µg/min per each episode of angina	OL, OS Patients with angina at rest unresponsive to standard therapy including oral or topical nitrates and β-blockers	N=35 24 hours	Primary: Clinical response Secondary: Not reported	Primary: NTG therapy reduced the number of episodes of angina at rest from 3.5±0.4 to 0.3±0.1, reduced doses of sublingual NTG from 1.9±0.3 to 0.4±0.1 mg/day and decreased morphine sulfate use from 5.5±1.3 to 0.4±0.2 mg/day (P<0.001 for all). Complete response, defined as no rest angina, was achieved in 25 patients, while eight patients experienced greater than a 50% reduction in episodes and two patients where nonresponders. Secondary: Not reported
Karlberg et al.[46] (1998) NTG IV titrated from 1.5 mL/hour	DB, PC, RCT Patients with recent onset of chest pain, suggestive of	N=143 48 hours	Primary: Reduction in ongoing signs of myocardial ischemia,	Primary: Treatment with NTG IV resulted in fewer patients (13) experiencing ongoing signs of ischemia (AP1 + AP2) than placebo (25; P<0.03). There were significantly less patients on active treatment that required >2 sublingual NTG tablets compared to placebo (12 vs 22; P<0.005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in <1 hour to a maximum of 12 mL/hour vs placebo	myocardial ischemia or worsening of previously stable angina pectoris and clinical evidence of underlying CAD		leukocyte activation, inhibition of platelet aggregation Secondary: Adverse effects	There was no significant difference found between groups in regards to leukocyte activation or inhibition of platelet aggregation. Secondary: Active treatment was stopped in seven patients compared to zero in the placebo group (P<0.001). Five patients terminated therapy prematurely because of headache while two patients stopped because of a decrease in BP and bradycardia.
Heart Failure				
Cohn et al.[47] (1986) V-HeFT I ISDN 160 mg/day and hydralazine 300 mg/day vs prazosin 20 mg/day vs placebo	AC, DB, PC, RCT Men with impaired cardiac function and reduced exercise tolerance on digoxin and a diuretic	N=642 3 years	Primary: Mortality Secondary: Effect on left ventricular function	Primary: There was a 34% risk reduction in mortality by two years in the ISDN plus hydralazine group compared to placebo (P<0.028). Cumulative mortality rates of 25.6 and 36.2% were observed in the ISDN plus hydralazine group at two and three years respectively, compared to 34.3 and 46.9% in the placebo group. The results found in the prazosin group were similar to placebo. Secondary: A significant increase in the LVEF was reported at eight weeks and one year in the ISDN plus hydralazine treatment group, but not in either the prazosin or placebo groups.
Cohn et al.[48] (1991) ISDN 40 mg QID and hydralazine 75 mg QID (individual agents, concurrent therapy) vs	AC, DB, RCT Men with heart failure (primarily NYHA class II and III), receiving digoxin and diuretics	N=804 2 years	Primary: All-cause mortality Secondary: Not reported	Primary: The results demonstrated significantly lower mortality after two years with enalapril (18%) vs ISDN and hydralazine (25%; P=0.016). In addition, overall mortality tended to be lower with enalapril vs ISDN and hydralazine (P=0.08). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
enalapril 10 mg BID				
Taylor et al.[49] (2004) A-HeFT ISDN 20 mg TID and hydralazine 37.5 mg TID, increased to ISDN 40 mg TID plus hydralazine 75 mg TID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for ≥3 months and evidence of left ventricular dysfunction within the prior 6 months	N=1,050 Mean duration of follow-up was 10 months	Primary: A composite score made up of weighted values for death from any cause, a first hospitalization for heart failure, quality of life changes Secondary: Not reported	Primary: Combination of vasodilators in addition to standard therapy had significant mortality benefit (mortality rate of 6.2 vs 10.2%; P=0.02). From a range of possible scores of -6 to 2, patients in the active treatment group achieved a significantly better score of -0.1±1.9 compared to -0.5±2.0 in the placebo group (P=0.01). Each separate value of the composite score was also significantly better in the active group when compared to placebo. There was a 43% decrease in the rate of death from any cause (HR, 0.57; P=0.01), and a 33% reduction in the rate of first hospitalizations (P=0.001). This led to the early termination of the trial. Additionally, there was a significant improvement in quality of life scores found with ISDN plus hydralazine when compared to placebo (-5.6±20.6 vs -2.7±21.2; P=0.02). Secondary: Not reported
Taylor et al[50] (2007) A-HeFT ISDN 20 mg TID and hydralazine 37.5 mg TID, increased to ISDN 40 mg TID and hydralazine 75 mg TID vs placebo	Post-hoc analysis of A-HeFT Patients ≥18 years of age, self-identified as of African descent, with NYHA class III or IV heart failure on standard therapy for ≥3 months and evidence of left ventricular dysfunction within the prior 6 months	N=1,050 Mean duration of follow-up was 18 months	Primary: Cause specific mortality, event free survival (time to either death or first hospitalization and time to first hospitalization for heart failure Secondary: Subgroup analysis	Primary: Cardiovascular deaths were significantly reduced in the treatment group compared to the placebo group (5.0 vs 8.5%; P=0.027). Pump failure death was also significantly reduced (75%) compared to the placebo group (0.8 vs 3.0%; P=0.012). There were no significant differences between the groups for other causes of death. In the treatment group event-free survival (death or first hospitalization for heart failure) was significantly improved compared to the placebo group (HR, 0.63; 95% CI, 0.49 to 0.81; P<0.001). The time to first hospitalization for heart failure was also significantly reduced (HR, 0.61; 95% CI, 0.46 to 0.80; P<0.001). Secondary: A consistent beneficial effect was seen in the treatment sub groups (age,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sex, baseline BP, history of chronic renal insufficiency, presence of diabetes, cause of heart failure, and baseline medication use) on primary composite score and event-free survival.
Yancy et al[51] (2007) X-A-HeFT ISDN 20 mg TID and hydralazine 20 mg TID, titrated up to ISDN 40 mg TID and hydralazine 75 mg TID vs placebo	ES, OL Patients previously enrolled in A-HeFT with NYHA class I to IV heart failure symptoms while receiving background therapy and satisfying the A-HeFT inclusion criteria	N=158 12 months or until ISDN-hydralazine approved by the FDA	Primary: Compliance with study drug, safety, tolerability Secondary: Change in NYHA association class, death, hospitalization for heart failure	Primary: Compliance in the treatment group averaged 87±25%, with no significant difference when compared to the placebo group. There were no significant differences in adverse events between the groups. Secondary: No significant difference was seen in hospitalizations from heart failure according to randomization. The greatest improvement in heart failure symptoms occurred in NYHA class III (at baseline) compared to other classes (P<0.001). Overall most patients were unchanged with 24% showing improved NYHA class and 9% showing a worsening.

Drug regimen abbreviations: BID=twice daily, ER=extended-release, ISDN=isosorbide dinitrate, ISMN=isosorbide mononitrate, IV=intravenous, NTG=nitroglycerin, QID=four times daily, TID=three times daily
Study abbreviations: AC=active comparator, DB=double-blind, ES=extended study, MC=multicenter, OL=open-label, OS=observational, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, XO=cross-over
Miscellaneous abbreviations: BP=blood pressure, CAD=coronary artery disease, DBP=diastolic blood pressure, FDA=Food and Drug Administration, HR=hazard ratio, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, SBP=systolic blood pressure, UA=unstable angina

Additional Evidence

Dose Simplification
Kardas et al evaluated adherence rates with once daily isosorbide mononitrate compared to twice daily isosorbide mononitrate over the course of 10 weeks. Adherence rates were significantly better with the once daily regimen compared to the twice daily regimen (P<0.001). The once daily regimen also led to a significant reduction in the mean weekly number of chest pain episodes compared to the twice-daily regimen (P<0.0001).[52] Brun et al evaluated adherence with a once daily and twice daily formulation of isosorbide mononitrate in patients with stable angina. Adherence rates were better with the once daily regimen compared to the twice daily regimen. The improvement in adherence also resulted in fewer angina episodes and a reduction in the number of nitroglycerin tablets that were taken to treat acute angina attacks.[53]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Nitrates and Nitrites

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Isosorbide dinitrate	extended-release capsule, extended-release tablet, sublingual tablet, tablet	Dilatrate-SR®, Isordil®, Isordil Titradose®*	$-$$$$$	$
Isosorbide mononitrate	extended-release tablet, tablet	Imdur®*, Monoket®*	$$$-$$$$	$
Nitroglycerin	injection, ointment, sublingual tablet, transdermal patch, translingual spray	Minitran®*, Nitro-Bid®, Nitro-Dur®*, Nitrolingual®*, Nitrostat®, Nitromist®*	$	$$

*Generic is available in at least one dosage form or strength.
†Product was added to Medicaid's drug file after the meeting's drug list was approved.
N/A=Not available.

X. Conclusions

The nitrates and nitrites are approved for the acute, prophylactic and chronic treatment of angina. In addition, intravenous nitroglycerin is approved for the control of congestive heart failure in the setting of myocardial infarction, for the induction of intraoperative hypotension, and for the treatment of perioperative hypertension.[2-12] All of the nitrate and nitrite products are available in a generic formulation.

There are several organizations that provide recommendations on the use of the nitrates and nitrites. Sublingual nitroglycerin tablets and nitroglycerin spray are recommended for the immediate relief of angina in all patients. For the treatment of chronic angina, β-blockers are recommended as first-line therapy. Long-acting calcium channel blockers or long-acting nitrates may be used if initial therapy is not successful, or if β-blockers are contraindicated. Combination therapy may be necessary in certain patients. The combination of β-blockers and long-acting nitrates are preferred due to their efficacy and safety.[16-20] Nitrates have not demonstrated a reduction in mortality in patients with coronary artery disease or following a myocardial infarction.[28,29] Sublingual and intravenous nitroglycerin is recommended for the acute treatment of unstable angina, myocardial infarction, and acute coronary syndrome in addition to standard therapy. For the treatment of heart failure, angiotensin converting enzyme (ACE) ACE inhibitors, β-blockers, and diuretics are the cornerstone of therapy. The combination hydralazine and a nitrate is an alternative treatment option in patients with heart failure who have reduced left ventricular ejection function when ACE inhibitors or angiotensin II receptor blockers are not tolerated. Furthermore, the combination hydralazine and a nitrate is recommended to improve outcomes for patients self-described as African American who have moderate to severe symptoms on optimal therapy with ACE inhibitors, β-blockers, and diuretics. The addition of hydralazine and a nitrate is reasonable for patients with heart failure who are already taking an ACE inhibitor and β-blocker for symptomatic heart failure, but who have persistent symptoms.[21,22,24,25,28-34 13]

Since all nitrates have similar pharmacologic effects, product selection is based on the desired onset and duration of action. Tolerance develops after chronic exposure to nitrates, regardless of the route of administration or formulation used. This can be overcome by instituting short periods (10 to 12 hours) of withdrawal from nitrate therapy.[2-14]

There is insufficient evidence to support that one brand nitrate or nitrite product is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand nitrates or nitrites within the class reviewed are comparable to each other and to the generics and over-the-counter products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand nitrate or nitrite is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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